

American

Heart Journal

International Editorial Board

I. A. Ahlberg	Salt Lake City
R. P. Ahlquist	Augusta
S. Gilbert Blount, Jr.	Denver
Ives Bouvraïn	Paris
A. Braun	Jerusalem
Daniel A. Brody	Stemphie
Agustin Castellanos, Jr.	Miami
Henri Chevalier	Paris
M. r. Clapper	Detroit
James A. Cronvich	New Orleans
Arthur C. DeGraff	New York
Lewis Dexter	Boston
Leonard S. Dreifu	Philadelphia Pa
Jesse E. Edwards	St Paul
Alvan R. Feinstein	New Haven Conn
M. Irene Ferrer	New York
Ch. r. F. ch	Indianapolis
J. l. an. i. eden	New Rochelle N Y
Peter C. Gazez	Ch. l. l. l. on
A. Sidney Harris	New Orleans
George M. Has	Chicago
Frank ek Herles	Prague Czechoslovakia
Paul Hugenholtz	Rotterdam
Harold A. Kahn	Bethesda
P. i. k. orner	Sydney
Richard Langendorf	Chicago
Maurice Lev	Chicago
Robert L. Levy	New York
Howard I. Lewis	Portland Ore
R. J. Linden	Leeds
F. Loozen	Dusseldorf Germany
Daniel S. Lukas	New York
Pavel E. Lukomsky	Moscow
Dan. ht C. McGoon	Rochester Minn
Felipe Mendoza	Mexico D F Mex
Gordon h. Moe	Osaka Y J
Clifford A. Nelson	Portland Me
Edward S. Organ	Durham
Victor I. ar. o. met	Newark
Joseph h. Fe. l. off	Washington D C
Alfred Pick	Chicago
Walter H. Fritchard	Cleveland
Simon Rodbard	Dun. le
Ralph C. Scott	Cincinnati
Ewald E. Selkurt	Indianapolis
Arthur Selzer	San Francisco
John T. Shepherd	Rochester Minn
I. P. Shillingford	London
Ernst Simonson	Minneapolis
John R. Smith	St Louis
Louis A. Soloff	Philadelphia
Aly H. Sorour	Cairo
Madison J. Spieh	Du. ham
David H. Spodnick	Boston
J. k. L. Titus	Rochester Minn
Tatuya Tomomatsu	Kobe Japan
William H. Wadman	Rochester Minn
Myron W. Wheat, Jr.	Lou. ville
Henry A. Zimmerman	Cleveland

GEORGE E. BURCH *Editor*

HARRY L. COLCOLOUGH

JOHN H. PHILLIPS *Assistant Editors*

THE C. V. MOSBY COMPANY *Publishers*
St. Louis Mo. 63141 USA

An international
publication
for the study of
the circulation

Contents on pp. 3, 5 and 7

Contents

Editorial

Hypertension in children 1

Sol Lorde MD and David Goldring MD St Louis Mo

Clinical communications

Blood pressures of Kung bushmen in Northern Botswana 5

*A S Truswell MB ChB MD MRCP B V Fennelly
MB ChB PhD MRCP J D L Hansen MB ChB MD
FRCP DCH and R B Lee MA PhD Cape Town and
Johannesburg South Africa and Cambridge Mass*

Cardiomyopathy without cardiomegaly in alcoholics 13

*Santharan K Asokan MD Martin J Frank MD and
A Calhoun Wigham MD Augusta Ga*

Rules for the diagnosis of visceral situs truncocoanal morphologies
and ventricular inversions 19

*Maria V de la Cruz MD and Bernardo Nadal Ginard MD
Mexico City Mexico*

Pulmonary cineangiography in acute pulmonary embolism 33

*Steven G Meister MD Harold L Brooks MD Murrill W Suss MD
John S Banas Jr MD Lewis Dexter MD and
James E. Dalen MD Boston Mass*

Incomplete bilateral bundle branch block and A V block complicating
acute anterior wall myocardial infarction 38

Sidney Fenig MD and Edgar Lichtstein MD New York N Y

Left anterior hemiblock and right bundle branch block before
and after surgical repair of tetralogy of Fallot 45

*Elliot Chesler MD (Rand) FRCP (Edin) FACC
Walter Beik V Sc M Med MRCP FACC and
Velva Schrire V Sc PhD MD FRCP FRCPE FRCP FACC
Cape Town South Africa*

Experimental and laboratory reports

Exchangeable potassium in heart disease Long term effects
of potassium supplements and amiloride 53

*M S Crismon MB MRACP J M Hewitt MD FRACP
and M B John B Sc Auckland New Zealand*

A critical examination of the validity of the use of vein
grafts in treating ischemic heart disease 61

Masayoshi Yokoyama MD Tokyo Japan

**“The drug of choice
for oral replacement
of potassium is
potassium chloride
solution.”**

AMA Drug Evaluations 1971 First Edition
Chicago: American Medical Association p. 121

**Kay Ciel® Elixir is
potassium chloride...
tastes good too!**

COMPOSITION Each 15 cc (one tablespoonful) contains potassium chloride 15 Gm, supplying 20 mEq. of elemental potassium in a cherry flavored palatable base alcohol 4%. Contains no sugar.

INDICATIONS Treatment of potassium deficiency occurring especially during thiazide diuretic or corticosteroid therapy; digitalis intoxication; low dietary intake of potassium or as a result of excessive vomiting and diarrhea.

CONTRAINDICATIONS Impaired renal function; untreated Addison's Disease; dehydration; heat cramps; and hyperkalemia.

PRECAUTIONS Potassium chloride should be administered with caution and adjusted to the requirements of the individual patient, since the amount of deficiency and corresponding daily dose is

often not known. Excessive or even therapeutic dosages may result in potassium intoxication. Patients should be frequently checked and periodic ECG and/or plasma potassium levels made. High plasma concentrations of potassium ion may cause cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease. In hypokalemic states attention should be directed toward the correction of the frequently associated hypochloremic alkalosis.

SIDE EFFECTS Vomiting, nausea, abdominal discomfort and diarrhea may occur. Symptoms and signs of potassium intoxication include listlessness, mental confusion, paresthesia of the extremities, weakness of the legs, flaccid paralysis, fall in blood pressure, cardiac arrhythmias and heart block. When hyperkalemia

exists, it should be promptly treated with the discontinuance of potassium administration or other steps to lower serum levels, if indicated, since sudden shift in plasma levels may induce potentially dangerous cardiac arrhythmias.

DOSAGE AND ADMINISTRATION Adults: one tablespoonful (15 cc) diluted in one glass of water, twice daily after the morning and evening meal. Larger doses may be indicated according to the individual patient's requirements but should be administered under close supervision due to the possibility of potassium intoxication. Patients should be cautioned to follow directions explicitly in regard to dilution of Kay Ciel Elixir to prevent gastrointestinal injury.

HOW SUPPLIED One pint and one gallon bottles.

Coper

Coper Laboratories Inc. Wayne, N.J. 07470/St. Therese, P.Q., Canada

Contents *continued*

Angina pectoris and slow flow velocity of dye in coronary arteries—A new angiographic finding 66

A. A. Tambe MD, M. A. Demany MD, Henry A. Zimmerman MD and E. Mascarenhas MD, Cleveland, Ohio

The relation between the conductivity of the blood and the body tissue and the amplitude of the QRS during heart filling and pericardial compression in the cat 72

Mordechai Manogch V. Sc. Eng., Simon Geller Ph.D. MD, Ednah Grestman M.Sc. and Deliah Laron B.Sc., Tel Aviv, Israel

Interrupted eccentric longitudinal muscle fibers of the kidney and adrenal veins 76

Huifang M. Payan MD and Enid F. Gübert MD, Ishpeming, Mich.

Experimental myocardial infarction in unanesthetized monkeys 82

John D. Hill D.V.M., M. Med. Sci., Manuel R. Malinow MD, Yuhua P. Mercury MD and A. John Dehner III B.S., Beaverton and Portland, Ore.

Case reports

Friedreich's ataxia associated with idiopathic hypertrophic subaortic stenosis 95

David G. Ruzhkhaupt MD, Otto G. Thilenius MD, Ph.D. and Donald E. Cassels MD, Chicago, Ill.

Congenital pulmonary and subclavian arteries steal syndrome 103

Reddy V. Shaher MD, Paul Patterson MD, Allan Stranahan MD, Thomas O. Der J. D., Matthew Farina MD and Monica Bishop MD, Albany, N.Y.

continued on page 7

Vol. 44, No. 1, July 1972. The American Heart Journal is published monthly by The C. V. Mosby Company, 11830 W. 11th, St. Louis, Mo. 63141.

A national subscription service

	U.S.	Canada	Other countries
1 year (12 issues)	\$25.50	\$ 8.50	\$ 7.25
2 years (24 issues)	\$49.50	\$ 16.50	\$14.25
3 years (36 issues)	\$73.65	\$24.65	\$21.40

Subscription prices are \$3.50 per copy. Remittances should be made by check, draft, post office or express money order payable to this Journal.

Subscriptions outside the United States and possessions are available to public and private libraries, schools, hospitals and clinics by mail to the provincial distributional government bureau and departments and all commercial and institutional organizations.

For annual subscription and all other rates subscription may be placed in names of and billed to individuals.

Subscription may begin at any time.

Second class postage paid at St. Louis, Mo.

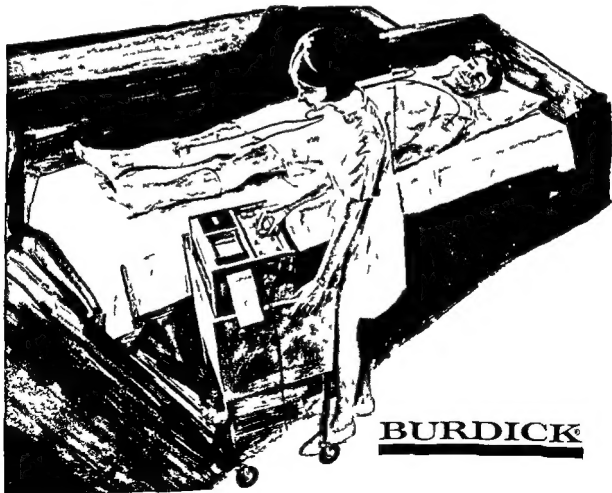
Printed in the U.S.A. Copyright © 1972 by The C. V. Mosby Company

why a Burdick Electrocardiograph?

Burdick's fully transistorized EK/5 has established a new level of ECG excellence, exceptional diagnostic accuracy and definition — changing long-standing concepts of ECG-patient environment. Make a careful point-by-point inspection of the results and you'll agree.

Ask for a direct comparison of Burdick EK/5 tracings with tracings from your present ECG equipment, or with tracings from any other cardiograph. You'll see the difference: greater response to both high and low frequencies.

Improvement and refinement are a continuing effort at Burdick. Ask your Burdick dealer for a thorough demonstration of the EK/5 so that you can determine to your satisfaction that the measure of an electrocardiograph is the electrocardiogram, or write us, The Burdick Corporation, Milton, Wisconsin 53563.



BURDICK®

Contents *continued*

Clinical pathologic conference

Clinical pathologic conference 110

Robert A. Van Tassel M D Kurt Amplatz M D

James H. Moller M D Franklin H. Martin M D and

Jesse E. Edwards M D St Paul Minn

Fundamentals of clinical cardiology

Incidence of persistent atrial fibrillation and
conduction defects in coronary heart disease 120

G. Orndahl M D O. Thulén M D and B. Hood M D

Göteborg Sweden

Appraisal and reappraisal of cardiac therapy

The medical treatment of angina pectoris II Design of an
antianginal drug study 132

Wilbert S. Aronow M D Long Beach and Irvine Calif

Annotations

Hazards of central venous pressure monitoring Pericardial
tamponade 135

Howard D. Homesley M D and John S. Zelenik M D

Nashville Tenn

Use of indicator dilution techniques to determine patency
of internal mammary artery implants 136

Grady H. Hendrix M D and William C. Maloy M D

Charleston S C

Acute elemental phosphorus poisoning in man Cardiovascular
toxicity 139

Robert C. Talley M D Joseph W. Lankast M D Alphonso J. Trevino M D

Linda Moore B A and Barry M. Beller M D San Antonio Texas

Angle of traction of the papillary muscle in normal and
dilated hearts A theoretic analysis of its importance in
mitral valve dynamics 141

G. E. Burch M D and T. D. Giles M D New Orleans La

Letters to the Editor

Comment on improved maneuver for left heart catheterization 145

Vladir Maranhao M D Browns Mills N J

Book reviews

Book reviews 146

Books received

Books received 147

Announcements

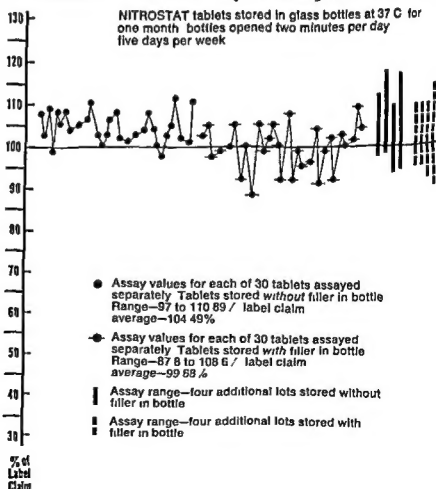
Announcements 148

Introducing Nitrostat™ (nitroglycerin) "potency-protected" sublingual nitroglycerin tablet

Thanks to a unique manufacturing process Parke Davis now offers a stabilized sublingual nitroglycerin tablet of more uniform potency. Migration of nitroglycerin into packaging materials and from one tablet to another is reduced. Your angina patients can count on more predictable dosage—something often not possible with conventional sublingual tablets.

NITROSTAT is the potency protected sublingual nitroglycerin you should prescribe. Available in 0.3 mg (1/200 gr), 0.4 mg (1/150 gr) and 0.6 mg (1/100 gr) sublingual tablets in color and symbol coded bottles.

Nitrostat uniform potency retention



PARKE-DAVIS
PARKE DAVIS & COMPANY
Detroit, Michigan 48232

Contents

Editorial

The problems of deep vein thrombosis 149

N L Browse MD FRCS London England

Clinical communications

Racial variations in the childhood electrocardiogram

Preliminary observations 153

*Daniel V Masica MD Barry J Maron MD L Jerome Krocet MD PhD
Baltimore Md*

Factors influencing hemolysis in valve prosthesis 161

*Carlos Crexells MD Nicolas Aeruchide MD Yvette Bonny MD Gilles Lepage MD
and Lucien Camptrou MD Montreal Canada*

The incidence of hypertension and associated factors

The Israel ischemic heart disease study 171

*Harold A Kohn MA Jack H Medalie MD MPH Henry N Neufeld MD
Egon Riss MD MSc and Uri Goldbourt MA Jerusalem Isael*

Prognostic value of an electrocardiographic sign in
acute myocardial infarction 183

M Afzal Mir MB BS DCH FRCP Kent England

Interrelationship of hemodynamic alterations of valvular heart disease
and renal function Influences on renal sodium reabsorption 189

*George A Porter MD Frank E Kloster MD J David Bristow MD and
Herbert E G Israel MD Portland Ore*

Experimental and laboratory reports

Comparison of the effects of two anesthetic agents on the
production of hypoxic pulmonary hypertension in dogs 203

*Armando Sarmiento MD Mitchell Passovey MA and Richard A Carleton MD
Chicago Ill*

The effects of dopamine on depressed myocardial function following
coronary embolization in the closed-chest dog 208

*Har y Lipp MBBS MRACP Raul E. Falcov MD Leon Resnekov MD FRCP
and Sheila King Chicago Ill*

**“The drug of choice
for oral replacement
of potassium is
potassium chloride
solution.”**

AMA Drug Evaluations 1971 First Edition
Chicago American Medical Association p 121

**Kay Ciel® Elixir is
potassium chloride...
tastes good too!**

COMPOSITION Each 15 cc (one table spoonful) contains potassium chloride 11 Gm. supplying 20 mEq. of elemental potassium in a cherry flavored palatable base acohol 4% Contains no sugar

INDICATIONS Treatment of potassium deficiency occurring especially during thiazide diuretic or corticosteroid therapy digitalis intoxication low dietary intake of potassium or as a result of excessive vomiting and diarrhea

CONTRAINDICATIONS Impaired renal function untreated Addison's Disease dehydration heat cramp and hyperkalemia

PRECAUTIONS Potassium chloride should be administered with caution and adjusted to the requirements of the individual patient since the amount of deficiency and corresponding daily dose is

often not known Excessive or even therapeutic dosages may result in potassium intoxication Patients should be frequently checked and periodic ECG and/or plasma potassium levels made High plasma concentrations of potassium ion may cause cardiac depression arrhythmias or arrest Use with caution in patients with cardiac disease In hypokalemic states attention should be directed toward the correction of the frequently associated hypochloremic alkalosis

SIDE EFFECTS Vomiting nausea abdominal discomfort and diarrhea may occur Symptoms and signs of potassium intoxication include listlessness mental confusion paresthesia of the extremities weakness of the legs flaccid paralysis fall in blood pressure cardiac arrhythmias and heart block When hyperkalemia exists

it should be promptly treated with the discontinuance of potassium administration or other steps to lower serum levels If indicated since sudden shift in plasma levels may induce potentially dangerous cardiac arrhythmias

DOSAGE AND ADMINISTRATION Adults one tablespoonful (15 cc.) diluted in one glass of water twice daily after the morning and evening meal Larger doses may be indicated according to the individual patient's requirements but should be administered under close supervision due to the possibility of potassium intoxication Patients should be cautioned to follow directions explicitly in regard to dilution of Kay Ciel Elixir to prevent gastrointestinal injury
HOW SUPPLIED One pint and one gallon bottles

Cooper

Cooper Laboratories Inc Wayne NJ 07470/St. Therese P.Q. Canada

Contents *continued*

Effect of caffeine on the ventricular fibrillation threshold in normal dogs and dogs with acute myocardial infarction 215

*Samuel Bellet MD Eckhard Horstmann MD Laurian R Roman MD
Norberto T DeGuzman MD and John B Kostis MD Philadelphia Pa*

Antinuclear antibody response to procainamide in man and laboratory animals 228

*Senga Whittingham MB ChB DCP PhD Ian R Mackay MD FRCP FRACP
Judith A Whitworth MB FRACP and Graeme Sloman MB BSc FRCP (Edin)
FRACP MRCP (Lond) FACC Victoria Australia*

Case reports

Diagnosis and treatment of a case of recurrent ventricular tachycardia 235

*William H Barry MD Edwin L Alderman MD Pat O Dady MD and
Donald C Harrison MD FACC Stanford Calif*

Double outlet right ventricle with left ventricular right atrial communication. Fibrous obstruction of left ventricular outlet by membranous septum and tricuspid leaflet tissue 242

*Andrew L Vezarity MD Richard G Chambers MD A Louise Calder MD
Stella Van Praagh MD and Richard Van Praagh MD
Fort Worth Texas and Boston Mass*

Azotemic arteriopathy 250

*Herman Rosen MD FACP Sandor A Friedman MD Albert E Rosner MD and
Auri Gerstmann MD Brooklyn NY*

Review

Pathogenesis of cardiac hypertrophy in coronary atherosclerosis and myocardial infarction 256

Henry S Bader MD Omaha Neb

continued on page 7

VOLUME 2 August 1972 The American Heart Journal is published monthly by The C.V. Mosby Company
11830 Westfield Drive St. Louis, Missouri 63141
All rights reserved.

	U.S.	Canada M	Other countries
Institutional	\$ 5.50	\$ 6.00	\$29.25
Personal	\$19.50	\$22.50	\$23.25
Student (not for resale)	\$13.65	\$16.65	\$17.40

Subscription price \$33.00 per year. Remittances should be made by check, draft, post office order, or express money order payable to the Journal.

Individual (multiple) subscriptions are available to public and private libraries, schools, hospital and city, county, state, provincial, and national government bureaus and departments and all commercial and professional subscriptions.

For all subscriptions and all rates, subscription must be in the name of and billed to individuals.

Second class postage paid at St. Louis, Mo.

Printed in the U.S.A. Copyright © 1972 by The C.V. Mosby Company

AVAD- EN 2471 1 FAE
2011

Kay Ciel Elixir is potassium chloride... tastes good too!

[illegible]

Open

44-38861-1000

Contents

Editorial

The problems of deep vein thrombosis 149

A L Browse MD FRCS London England

Clinical communications

Racial variations in the childhood electrocardiogram

Preliminary observations 153

*Daniel V Masco MD Barry J Varon MD L Jerome Krovit MD PhD
Baltimore Md*

Factors influencing hemolysis in valve prosthesis 161

*Carlos Craxells MD Nicolas Aeriche MD Lucille Bonny MD Gilles Lepage MD
and Lucien Campeau MD Montreal Canada*

The incidence of hypertension and associated factors

The Israel ischemic heart disease study 171

*Harold A Kahn MA Jack H Medalie MD MPH Henry N Neufeld MD
Egon Rus MD MSc and Uri Goldbourt MA Jerusalem Israel*

Prognostic value of an electrocardiographic sign in

acute myocardial infarction 183

M Afzal Mir MB BS DCH MRCP Kent England

Interrelationship of hemodynamic alterations of valvular heart disease
and renal function Influences on renal sodium reabsorption 189

*George A Porter MD Frank E Kloster MD J David Bruston MD and
Herbert E Gissel MD Portland Ore*

Experimental and laboratory reports

Comparison of the effects of two anesthetic agents on the
production of hypoxic pulmonary hypertension in dogs 203

*Amando Susmano MD Mitchell Passovoy MA and Richard A Carleton MD
Chicago Ill*

The effects of dopamine on depressed myocardial function following
coronary embolization in the closed-chest dog 208

*Harry Lipp MBBS MRACP Raul E Falster MD Leon Resnekov MD FRCP
and Sheila King Chicago Ill*

**"The drug of choice
for oral replacement
of potassium is
potassium chloride
solution."**

AMA Drug Evaluations 1971 First Edition
Chicago: American Medical Association p 121

**Kay Ciel[®] Elixir is
potassium chloride...
tastes good too!**

COMPOSITION Each 15 cc (one table-
spoonful) contains potassium chloride 15
Gm, supplying 20 mEq. of elemental
potassium, in a cherry flavored palatable
base alcohol 4%. Contains no sugar.

INDICATIONS Treatment of potassium
deficiency occurring especially during
thiazide diuretic or corticosteroid therapy
of digitalis intoxication, low dietary intake
of potassium or as a result of excessive
vomiting and diarrhea.

CONTRAINDICATIONS Impaired renal
function, untreated Addison's disease,
dehydration, heat cramps, and hyper-
kalemia.

PRECAUTIONS Potassium chloride
should be administered with caution and
adjusted to the requirements of the indi-
vidual patient, since the amount of defi-
ciency and corresponding daily dose is

often not known. Excessive or even ther-
apeutic dosages may result in potassium
intoxication. Patients should be frequently
checked and periodic ECG and/or plasma
potassium levels made. High plasma con-
centrations of potassium ion may cause
cardiac depression, arrhythmias or arrest.
Use with caution in patients with cardiac
disease. In hypokalemic states, attention
should be directed toward the correction
of the frequently associated hypochloremic
alkalosis.

SIDE EFFECTS Vomiting, nausea,
abdominal discomfort and diarrhea may
occur. Symptoms and signs of potassium
intoxication include listlessness, mental
confusion, paresthesia of the extremities,
weakness of the legs, flaccid paralysis,
fall in blood pressure, cardiac arrhythmias
and heart block. When hyperkalemia

exists, it should be promptly treated with
the discontinuance of potassium adminis-
tration or other steps to lower serum levels.
If indicated, since sudden shift in plasma
levels may induce potentially dangerous
cardiac arrhythmias.

DOSAGE AND ADMINISTRATION Adults:
one tablespoonful (15 cc) diluted in one
glass of water, twice daily after the
morning and evening meal. Larger doses
may be indicated according to the indi-
vidual patient's requirements but should
be administered under close supervision
due to the possibility of potassium intoxi-
cation. Patients should be cautioned to
follow directions explicitly in regard to
dilution of Kay Ciel Elixir to prevent
gastrointestinal injury.

HOW SUPPLIED One pint and one gallon
bottles.

Cooper

Cooper Laboratories Inc. Wayne, N.J. 07470/Ste. Theresa P.O. Canada

Contents *continued*

Effect of caffeine on the ventricular fibrillation threshold in normal dogs and dogs with acute myocardial infarction 215

Samuel Bellet MD Eckhard Horstmann MD Laurian R Roman MD
Norberto T DeGuzman MD and John B Koster MD Philadelphia Pa

Antinuclear antibody response to procainamide in man and laboratory animals 228

Senga Whittingham MB ChB DCP PhD Ian R Mackay MD FRCP FRACP
Judith A Whitworth MB MRACP and Graeme Sloman MB BSc FRCP (Edin)
FRACP MRCP (Lond) FACC Victoria Australia

Case reports

Diagnosis and treatment of a case of recurrent ventricular tachycardia 235

William H Barry MD Edwin L Alderman MD Pat O Daily MD and
Donald C Harrison MD FACC Stanford Calif

Double-outlet right ventricle with left ventricular right atrial communication Fibrous obstruction of left ventricular outlet by membranous septum and tricuspid leaflet tissue 242

Andrew L Vengart MD Richard G Chambers MD A Louise Calder MD
Stella Van Praagh MD and Richard Van Praagh MD
Fort Worth Texas and Boston Mass

Azotemic arteriopathy 250

Herman Rosen MD FACP Sander A Friedman MD Albert E Rainer MD and
Auri Gerstmann MD Brooklyn N Y

Review

Pathogenesis of cardiac hypertrophy in coronary atherosclerosis and myocardial infarction 256

Henry S Bodeer MD Omaha Neb

continued on page 7

VOLUME 2 AUGUST 1972 The American Heart Journal is published monthly by The C.V. Mosby Company
11830 W. Chesterfield Drive St. Louis, MO 63141
A national journal of cardiology

	U.S.	Canada	Outside
Individual	\$25.50	\$28.50	\$29.25
Personal	\$19.50	\$22.50	\$23.25
Student/Institutional	\$13.65	\$16.65	\$17.40

Single copies are \$3.50 postpaid. Remittances should be made by check, draft, post office or express money order payable to this journal.

For multiple (multiple read) subscription rates, please apply to the publisher, The C.V. Mosby Company, 11830 W. Chesterfield Drive, St. Louis, MO 63141. For institutional subscription rates, please apply to the publisher, The C.V. Mosby Company, 11830 W. Chesterfield Drive, St. Louis, MO 63141.

Personal subscriptions and all student rate subscriptions must be billed to the publisher and billed to the publisher.

Subscriptions may begin at any time.
Second class postage paid at St. Louis, Mo.

Printed in the U.S.A. Copyright © 1972 by The C.V. Mosby Company

Dialose® Plus has no pits...

(dioctyl sodium sulfosuccinate and sodium carboxymethylcellulose plus casanthranol)



And no pitfalls, either, in the management of the constipated cardiac patient

Because Dialose Plus is more consistently reliable than the old fashioned constipation remedy

To lessen the strain of constipation, it provides the effective yet gentle peristalsis stimulation of casanthranol

And Dialose Plus softens and lubricates too for easier, less painful defecation

Also available Dialose® (dioctyl sodium sulfosuccinate and sodium carboxymethylcellulose)—for effective stool softening and lubrication when peristalsis stimulation is not required



STUART PHARMACEUTICALS | Pasadena, California 91109
Division of ATLAS CHEMICAL INDUSTRIES, INC.

Contents continued

Fundamentals of clinical cardiology

Functional diastolic murmurs 263

*Aldo A Luisada MD and Mohamed K A Dayem MD PhD MRCP
Chicago Ill*

Appraisal and reappraisal of cardiac therapy

Medical treatment of angina pectoris III

Pharmacology of sublingual nitrites as antianginal drugs 273

Rübert S Aronow MD Long Beach and Irvine Calif

Annotations

Double reset of demand pacemakers 276

S Serge Barold MB MRACP and Michael Carroll Rochester N Y

Reflex vasodilatation and Raynaud's disease 277

George E Burch MD New Orleans La

Assessment of LVEDP from right heart pressures during atrial pacing 279

Joseph W Linhart MD Philadelphia Pa

Einthoven G J Burch and the capillary electrometer 280

*Daniel A Brody John W Cox Jr Harry A Phillips and
Francis W Keller Memphis Tenn*

Letters to the Editor

The closing snap in mitral stenosis 282

Morton E Tavel MD and Harvey Feigenbaum MD Indianapolis Ind

Reply 293

Simon Rodbard MD Duarte Calif

Anticoagulants in pregnancy 284

Armand J Quick MD Milwaukee Wisc

Digitalis intoxication 285

Ufredo León Cárter MD Tegucigalpa Honduras

Book reviews

Book reviews 286

Books received

Books received 287

Announcements

Announcements 287

August, 1972

in cardiac edema*

Dyrenium®

brand of

triamterene

potassium-conserving diuretic

acts within 2 hours¹— a single day's administration can be given with good effect¹

usual dosage is one capsule twice daily— some patients may be maintained on one capsule daily or every other day. Since the action of Dyrenium is independent of aldosterone levels, dosage need not be increased as aldosterone builds up.

cost to your patient—22¢ or 11¢ per day— based on the cost to the patient for 30 capsules

Before prescribing, see complete prescribing information in SK&F literature or PDR.

***Indications:** Edema associated with congestive heart failure, cirrhosis and nephrotic syndrome, steroid-induced edema, idiopathic edema, edema due to secondary hyperaldosteronism and edema resistant to other diuretic therapy.

Contraindications: Severe or progressive kidney disease or dysfunction (possible exception: nephrosis). Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity to the drug. Continued use in developing hyperkalemia. Do not give potassium supplements either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy only when essential to patient welfare.

Dyrenium (triamterene, SK&F) and spironolactone are not

usually used concurrently if they are, however, frequent serum potassium determinations are required.

Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with anti-hypertensive drugs may result in an additive hypotensive effect. When Dyrenium is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

augments the effects of other diuretics— combined with another diuretic, Dyrenium can augment diuresis and natriuresis with lower doses of each agent.²

usually used concurrently if they are, however, frequent serum potassium determinations are required.

Adverse Reactions: Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.

Note: When combined with another diuretic, the initial dosage of each agent should be lower than recommended.

Supplied: 100 mg capsules in bottles of 100

1. Ross E.J. Aldosterone and Its Antagonists. *Clin Pharmacol & Therap* 65 (Jan-Feb) 1965.
2. Earley L.E. Edema Formation and the Use of Diuretics. *California Med* 114:56 (Mar) 1971.

Contents

Editorial

The cardiac patient and hemodynamics 289

Abraham Hoordergraaf Ph D Rotterdam and Delft The Netherlands

Clinical communications

Myxoid changes in cardiac valves pathologic clinical and ultrastructural studies 294

William H Kern MD and Bernard L Tucker MD Los Angeles Calif

Vectorcardiographic and electrocardiographic differentiation between cor pulmonale and anterior wall myocardial infarction 302

Yoshihiko Watanabe MD Kenji Nishijima MD Harold Richman MD and Ernst Simonson MD Minneapolis Minn

Localization of an area of maximum refractoriness or gate in the ventricular specialized conduction system in man 310

John J Gallagher MD Anthony N Damato MD P Jacob Varghese MD and Sun H Lau MD Staten Island N Y

A new roentgenographic assessment of anatomic deformity in calcific aortic stenosis 321

Paul D Stein MD Oklahoma City Okla

Ejection fraction in anomalous origin of the left coronary artery from the pulmonary artery 325

James A Menke Reda M Shaker MD and Grace S Welff MD Albany N Y

Experimental and laboratory reports

Levels of concealment in second degree and advanced second degree A V block 330

Yoshio Watanabe MD and Leonard S Delfus MD Philadelphia Pa

In vitro serum cholesterol esterification in coronary artery disease 348

Ilja old L Rutenberg MD Al n G Stern Louis A Soloff MD and S deB Braverman MS Philadelphia Pa

Effect of glucagon on automaticity threshold for stimulation and atrioventricular conduction in patients with impaired impulse formation or conduction 359

At a Nishimura MD R B Fortner MD and John F Williams J MD Galveston Texas

in cardiac edema^{*}

Dyrenium[®]

brand of

triamterene

potassium-conserving diuretic

acts within 2 hours¹ — a single day's administration can be given with good effect¹

usual dosage is one capsule twice daily — some patients may be maintained on one capsule daily or every other day. Since the action of Dyrenium is independent of aldosterone levels, dosage need not be increased as aldosterone builds up.

cost to your patient — 22¢ or 11¢ per day — based on the cost to the patient for 30 capsules

Before prescribing, see complete prescribing information in SK&F literature or PDR.

***Indications** Edema associated with congestive heart failure, cirrhosis and nephrotic syndrome; steroid-induced edema; idiopathic edema; edema due to secondary hyperaldosteronism and edema resistant to other diuretic therapy.

Contraindications Severe or progressive kidney disease or dysfunction (possible exception: nephrosis). Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity to the drug. Continued use in developing hyperkalemia. Do not give potassium supplements either by drug or by diet.

Warnings Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported. Check BUN and serum potassium periodically, especially in the elderly, diabetics and those with suspected or confirmed renal insufficiency. Use in pregnancy only when essential to patient welfare. Dyrenium (triamterene, SK&F) and spironolactone are not

usually used concurrently if they are, however, frequent serum potassium determinations are required.

usually used concurrently if they are, however, frequent serum potassium determinations are required.

usually used concurrently if they are, however, frequent serum potassium determinations are required.

usually used concurrently if they are, however, frequent serum potassium determinations are required.

usually used concurrently if they are, however, frequent serum potassium determinations are required.

usually used concurrently if they are, however, frequent serum potassium determinations are required.

usually used concurrently if they are, however, frequent serum potassium determinations are required.

Precautions If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with anti-hypertensive drugs may result in an additive hypotensive effect. When Dyrenium is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

Adverse Reactions Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.

Note When combined with another diuretic, the initial dosage of each agent should be lower than recommended.

Supplied 100 mg capsules in bottles of 100

1. Ross E.J. Aldosterone and Its Antagonists. *Clin Pharmacol & Therap* 6:65 (Jan-Feb) 1965.
2. Earley L.E. Edema Formation and the Use of Diuretics. *California Med* 114:56 (Mar) 1971.

SK&F CO
Carolina, PR 00630
A subsidiary of Smith Kline & French Laboratories

Contents *continued*

Effect of lidocaine on the scalar orthogonal electrocardiogram 366

Alan I Kermatier MD H Hayakawa MD and William J Mandel MD
Los Angeles Calif

Effects of ouabain on cardiac output and pulmonary blood flow in dogs 371

Elmer Treast MD Harley Ulano PhD Marc Pfeffer BA Walter Massion MD
Linda L Shandour PhD and Eugene D Jacobson MD
Oklahoma City Okla and Houston Texas

Ventricular responses to hypoxemia following
chemoreceptor denervation and adrenalectomy 377

Robert A Achter MD and S Evans Downing MD New Haven Conn

Case reports

External left atrial pulse tracings in extreme left atrial dilation 387

Nabil El Sherry MD and Zaki El Ramly MD Cairo Egypt U.A.R.

Postural hypotension in amyloid disease 395

B Gann MRCP MRCP E M P Mahoney MRCP D J Rowlands MRCP
and Alad W Jones D Path Manchester England

Clinical pathologic conference

Clinical pathologic conference 401

Robert A Schnitzler MD Jules Cohen MD Elliot O Lapchik MD and
Eric A Schenk MD Rochester N.Y.

Fundamentals of clinical cardiology

The jugular pulse in pericardial constriction Its differentiation
from that of cardiomyopathy 409

Charles P Liss MD Gary Hood MD and Morton E Tavel MD Indianapolis Ind

Appraisal and reappraisal of cardiac therapy

The medical treatment of angina pectoris IV Nitroglycerin
as an antianginal drug 415

Nahle S Aronow MD Long Beach and Irvine Calif

continued on page 7

VOLUME 3 September 1972 The American Heart Journal is published monthly by The C. V. Mosby Company
11530 Westline Industrial Drive St. Louis, Mo. 63141
A national circulation journal

	U.S.	Canada Mexico	Other countries
Individual	\$25.50	\$28.50	\$29.25
Personal	\$19.50	\$ 2.50	\$23.25
Student/Intern/Resident	\$13.65	\$16.65	\$17.40

Single copies \$3.50 per copy. Remittances should be made by check, draft, post office or express money order payable to this journal.

Individual (non-library) and institutional subscriptions are available to public and private libraries, schools, hospital and clinics, city, county, state, provincial and national government bureaus and departments and all commercial and private institutions and organizations.

Personal subscriptions are available to all students, residents, fellows, and all other individuals and are billed to the individual.

Subscriptions may begin at any time.

Second class postage paid at St. Louis, Mo.

Printed in the U.S.A. Copyright © 1972 by The C. V. Mosby Company

**"The drug of choice
for oral replacement
of potassium is
potassium chloride
solution."**

AMA Drug Evaluations 1971 First Edition
Chicago: American Medical Association p 121

**Kay Ciel[®] Elixir is
potassium chloride...
tastes good too!**

COMPOSITION Each 15 cc (one table-
spoonful) contains potassium chloride 15
Gm. supplying 20 mEq of elemental
potassium in a cherry flavored palatable
base alcohol 4%. Contains no sugar.
INDICATIONS Treatment of potassium
deficiency occurring especially during
thiazide diuretic or corticosteroid therapy
digitalis intoxication low dietary intake
of potassium or as a result of excessive
vomiting and diarrhea.

CONTRAINDICATIONS Impaired renal
function untreated Addison's Disease
dehydration heat cramps and hyper-
kalemia.

PRECAUTIONS Potassium chloride
should be administered with caution and
adjusted to the requirements of the indi-
vidual patient since the amount of defi-
ciency and corresponding daily dose is

often not known. Excessive or even ther-
apeutic dosages may result in potassium
intoxication. Patients should be frequently
checked and periodic ECG and/or plasma
potassium levels made. High plasma con-
centrations of potassium ion may cause
cardiac depression arrhythmias or arrest.
Use with caution in patients with cardiac
disease. In hypokalemic states attention
should be directed toward the correction
of the frequently associated hypochloremic
alkalosis.

SIDE EFFECTS Vomiting nausea
abdominal discomfort and diarrhea may
occur. Symptoms and signs of potassium
intoxication include listlessness mental
confusion paresthesia of the extremities
weakness of the legs flaccid paralysis
fall in blood pressure cardiac arrhythmias
and heart block. When hyperkalemia

exists it should be promptly treated with
the discontinuance of potassium adminis-
tration or other steps to lower serum levels.
If indicated since sudden shift in plasma
levels may induce potentially dangerous
cardiac arrhythmias.

DOSAGE AND ADMINISTRATION Adults
one tablespoonful (15 cc) diluted in one
glass of water twice daily after the
morning and evening meal. Larger doses
may be indicated according to the indi-
vidual patient's requirements but should
be administered under close supervision
due to the possibility of potassium intoxi-
cation. Patients should be cautioned to
follow directions explicitly in regard to
dilution of Kay Ciel Elixir to prevent
gastrointestinal injury.
HOW SUPPLIED One pint and one gallon
bottles.



Cooper Laboratories Inc. Wayne, N.J. 07470/St. Theresa #Q Canada

Contents *continued*

Annotations

On the chemical nature of basophilic (muconid) degeneration of myocardium 419

Juan Rotas MD St Louis Mo

Cardiac causalgia and hoarseness 420

G E Burch MD New Orleans La

Decline and fall? 420

Alexander R P Walker D Sc Johannesburg South Africa

Two hundredth anniversary of self prediction of sudden exertional cardiac death 422

Robert A Bruce MD Seattle Wash

Obituary

Velva Schrire MD FRCP FACC 1917-1972 424

Mervyn S Gotsman MD

Letters to the Editor

The reliability of the Holter Avionics system in reproducing the ST-T segment 427

Shlomo Stern MD and Dan Tzoni MD Jerusalem Israel

Hypertrophic obstructive cardiomyopathy 428

Lawrence A Jacobs MD Robert D Lee MD and

Paul N Yu MD Rochester N Y

Trends in training physicians 429

G E Burch MD New Orleans La

Atrioventricular interaction in isorhythmic dissociation 429

Karl W Diederich Priu Do MD and Hasib Djonlagic MD

Lubeck West Germany

Reply 431

Ka Ien L Paulay MD Anthony A Damato MD and

Gustav A Bobb BS Staten Island N Y

Book reviews

Book reviews 432

Books received

Books received 434

Announcements

Announcements 435

September 1972

Introducing the Burdick Compact Coronary Care Center designed and developed specifically for your budget, limited space, and cardiac procedures where unlimited mobility, versatility and full utilization are vital.

The Burdick CCCC is many things including reasonably priced

One Bed ICU Facility

Five inch screen monitor with Integral Heart Rate Meter automatic start electrocardiograph patient alarm capability mounted on mobile stand

Mobile Emergency Room

An emergency care station on wheels equipped with Cardiac Monitor HR meter DC Defibrillator EK/5 Electrocardiograph and mobile stand Cabinet space for essential drugs and supplies

Stress Exercise Monitoring

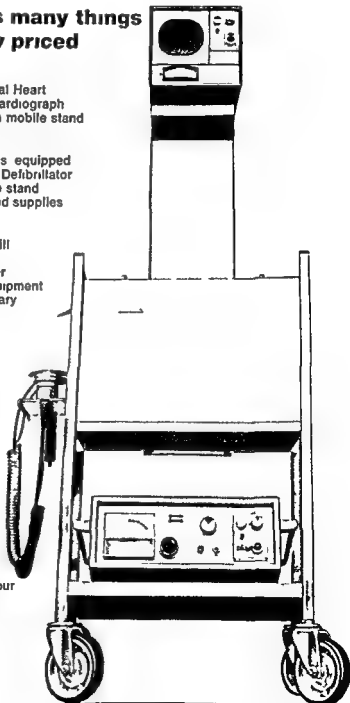
The value and importance of treadmill stress testing procedures lie in the detection of clinically unsuspected or silent coronary heart disease. Equipment required includes the Burdick Coronary Care Center plus a treadmill

Monitoring in Surgery

The CS/515 Monitor with Integral heart rate meter provides constant coronary surveillance of the patient with provision for automatic alarm and can accompany the patient to recovery room

Mobile Electrocardiograph

A highly mobile electrocardiograph for general bedside use anywhere in the hospital at a moment's notice. Solid state EK/5 provides new diagnostic capability and simplified operation. Equip your Burdick Compact Coronary Care Center for multi department flexibility that can be tailored to your specific needs. See your Burdick dealer or write The Burdick Corporation Milton Wis 53563



BURDICK®

Editor

GEORGE E BURCH M D

Assistant editors

HARRY L COLCOLOUGH M D

JOHN H PHILLIPS, M D

1430 Tulane Avenue

New Orleans Louisiana 70112

Publisher

THE C V MOSBY COMPANY

11830 Westline Industrial Drive

St Louis Missouri 63141

Editorial communications

Original communications Manuscripts for publication letters and all other communications relating to the editorial management of the Journal should be sent to the Editor Dr George E Burch 1430 Tulane Avenue New Orleans Louisiana 70112. Articles are accepted for publication with the understanding that they are contributed solely to the American Heart Journal.

Neither the editor nor the publisher accepts responsibility for the views and statements of authors whose manuscripts are published as original communications.

Manuscripts Manuscripts must be type written (on one side of the paper only) with liberal margins and completely double spaced except for mathematical material which must be triple spaced. When symbols cannot be inserted by the typewriter they must be clearly identifiable and carefully aligned. A list of References must appear at the end of the article following style used in the Cumulated Index Medicus and giving authors names and initials title and the name volume number page number and year of publication of the journal in that order. Illustrations accompanying manuscripts must be numbered provided with suitable legends and marked lightly on the back with the author's name. Submission of two copies of a manuscript and its illustrations will expedite editorial handling and speed publication.

Illustrations A reasonable number of halftone illustrations will be reproduced free of cost to the author but special arrangements

must be made with the editor for color plates elaborate tables or extra illustrations. To insure clear reproduction all copy for zinc cuts including pen drawings and charts must be prepared with India ink and a black ribbon must be used for type written material. Only good photographic prints and original drawings should be supplied for halftone work.

Exchanges Contributions letters exchanges reprints and all other communications relating to the Journal should be sent to Dr George E Burch 1430 Tulane Avenue New Orleans Louisiana 70112. Writers on subjects which are related in any way to cardiovascular disease are requested to place this address on their permanent reprint mailing lists.

Reprints Reprints of articles must be ordered directly through the publishers The C V Mosby Co 11830 Westline Industrial Drive St Louis Mo 63141 U S A who will quote prices upon publication of the article. Individual reprints of an article must be obtained through the author.

Review of books Publishers and authors are informed that the space of the Journal is so fully occupied by matter pertaining to the branches to which it is devoted that only works treating of these subjects can be noticed. Books and monographs on the anatomy physiology pharmacology therapeutics and pathology of the heart blood vessels and circulation will be reviewed when space is available. Send books to the Editor Dr George E Burch 1430 Tulane Avenue New Orleans Louisiana 70112.

Lanoxin
[digoxin]
(no substitution)



write it

precision quality control

- assured tablet content uniformity*
- predictable patient response
- proven biologic availability*

Contraindications There are no absolute contraindications to digitalis. However, in ventricular paroxysmal tachycardia or ventricular fibrillation, it should be used only in refractory cases not induced by digitalis intoxication and if heart failure has developed.

Precautions If the patient has been given digoxin during the previous week or any other less rapidly excreted drug of the digitalis group during the previous two weeks, the dose of Lanoxin brand Digoxin must be reduced accordingly. Because of impaired renal function and excretion in elderly patients, they frequently require lower than recommended doses.

Potassium loss in patients sensitizes the heart to digitalis intoxication even with recommended doses. The diuretic agents as well as electrolyte manipulations by the physician are major causes of potassium depletion in cardiac patients. Under these conditions, it may be necessary to reduce the usual dosages of Lanoxin brand Digoxin during digitalization and maintenance.

Digoxin is usually ineffective in cases of cardiac failure due to mechanical causes which are independent of myocardial diseases, e.g., cardiac tamponade or to disorders not primarily of cardiac origin, as severe anemia. Despite a variable or poor response to digoxin in the presence of active rheumatic carditis, the development of cardiac failure is an indication for its use.

Effects of Overdosage and Treatment The symptoms of overdosage with digoxin are quite similar to those occurring with other digitalis preparations. The most common toxic manifestations are anorexia, nausea, vomiting and various cardiac arrhythmias including ventricular extrasystoles and paroxysmal supraventricular tachycardia or fibrillation with A-V block. In general, the gastrointestinal manifestations of toxicity with digoxin precede the cardiac arrhythmias occurring from overdosage. Furthermore, because of the rapid dissipation of digoxin, manifestations of toxicity are of short duration, usually lasting from a few hours to one or two days.

If necessary, potassium chloride may be administered as an intravenous infusion containing (adult dosage) 40 milliequivalents in 500 cc. of 5% dextrose in water given over the course of 1 hour and repeated if required until a total of 120 milliequivalents have been given (1 mEq KCl = 74.5 mg). Electrocardiographic monitoring should be conducted and the infusion halted immediately upon the appearance of peaking of the T waves. For children, the intravenous infusion dosage of potassium chloride would be 5 to 10 milliequivalents in 100 cc. of 5% dextrose in water given over the course of 1 hour, repeated if required to a total of 15 to 30 milliequivalents. For more serious intoxication with abnormal cardiac rhythms, potassium chloride may be given orally in divided doses totaling 4 to 6 grams per day (adults) or 1 to 3 grams (children) provided renal failure is not present.

LANOXIN® digoxin TABLETS 0.125 mg (yellow) in bottles of 100 and 1,000; 0.25 mg (white) scored in bottles of 100, 500, 1,000 and 5,000; also Unit Dose Pack strips of 10 tablets, 10 boxes of 100 tablets (1,000); 0.5 mg (green) scored in bottles of 100 and 1,000.

Lanoxin® digoxin

Complete literature available on request from Professional Services Dept. PML



Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

Editorial

Hypertension in children

Sol Londe M D

David Goldring M D

St Louis Mo

The notion that hypertension of unknown etiology is uncommon in children has been commented upon in the pediatric literature for some time.¹⁻³ However in 1966 Tackeuchi⁴ after mass determinations of blood pressure in Japan reported that essential hypertension may start at an earlier age than was previously thought. More recently in February 1971 Zinner and his co-workers⁵ concluded from their studies that a familial influence on blood pressure can be detected in childhood and they postulated that the factors probably responsible for essential hypertension are acquired in childhood. The results of our recently published investigation⁶ of 74 hypertensive children add further evidence that this is probably the case.

At the beginning of our studies the definition of hypertension in childhood presented a problem. The published values for normal children varied widely and reliable standards for office practice were unavailable. It was therefore first necessary to establish normal values. The mean values, standard deviations, and the 80 and 90 percent ranges for each sex and year of age were calculated for systolic and diastolic pressures based on normal children examined in office practice. The population sample consisted of 795 boys and 798 girls 3 to

15 years of age. Appropriate size wrap around cuffs and the mercury sphygmomanometer were used and the pressures were obtained in a standard manner.^{7,10}

Our investigations on the hypertensive children were an outgrowth of the above studies and were conducted on 74 children 4 to 18 years of age who were asymptomatic and who either came for routine physical examinations to the private office of one of the authors (S L) or to his office in the Pediatrics Department of the St. Louis Labor Health Institute. The elevated pressures noted in these patients were incidental findings.

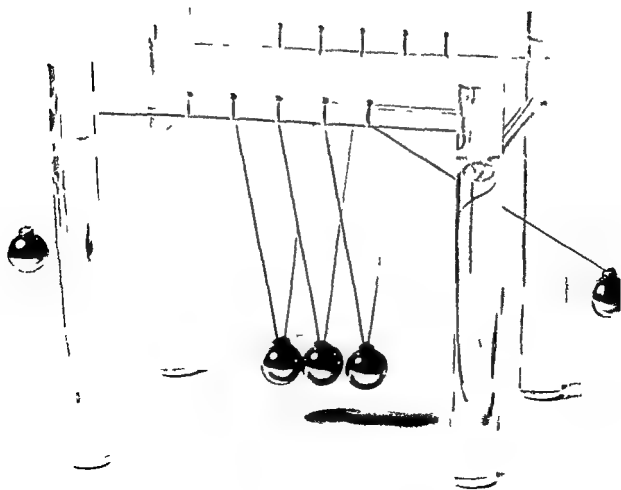
As suggested by Master and his co-workers¹¹ in their studies of adult patients children whose systolic and/or diastolic blood pressures were repeatedly recorded above the ninetieth percentile and occasionally above the ninety fifth percentile for age and sex were classified as hypertensive. All but 2 were under 15 years of age when their hypertension was first detected and they were followed for an average of 3½ years and in some cases for as long as 8 years. The youngest age at which elevated pressure was observed was 3 years. Only patients who were hypertensive for 1 year or longer were included in the study. Laboratory studies for possi-

From the Washington University School of Medicine, Edward Mall, Broad Department of Pediatrics Division of Cardiology, St. Louis Children's Hospital and the Pediatric Department of the St. Louis Labor Health Institute.
Received for publication May 26, 1971.
Reprint requests to Sol Londe, M.D., 7320 Colgate Avenue, St. Louis, MO 63130.

Alone among antiarrhythmics...

CARDIOQUIN tablets

quinidine polygalacturonate



was 3 years. Since we have documented elevated pressure as early as 3 years it is highly probable that hypertension may begin at an even earlier age. The necessity for establishing reliable blood pressure standards from early infancy to 3 years of age is obvious. There are now instruments available for the measurement of blood pressure in infancy¹³ and it is hoped that pediatricians will make use of these new techniques. Once reliable standards are established for this age group the question of how early hypertension appears may be answered.

The much higher incidence of hypertension and cardiovascular disease among black adults than among white leads to the question of how early in life this difference appears. Unfortunately there were not enough black children in the population studied by us to answer this question. Rose¹⁴ who compared black and white tenth grade children found no difference. Whether this is true for younger children awaits further investigation.

Our observations point to broader horizons for preventive pediatrics. The importance of spotting an early tendency to hypertension needs no emphasis to the readers of this Journal. However the importance of careful routine blood pressure determinations does need emphasizing to the practitioner treating children. The implications from the public health standpoint are clear. Furthermore just as the routine tuberculin test in the young sometimes leads to uncovering adult tuberculosis so may the finding of hypertension in children lead to the uncovering of hypertension in parents who may not have had blood pressure determination for a long time.

The studies herein discussed also indicate the necessity of continuing extramural research on healthy populations as well as continuing research in medical centers which concern themselves mainly with sick people. Only by continued observations of healthy infants and children will we be able to spot minor but significant deviations from the normal which may affect longevity.

The educational campaign on the concept of risk factors in atherosclerosis and

coronary artery disease which has been mounted by the American Heart Association has been aimed exclusively at the adult population. It may well be that both these diseases as well as essential hypertension have their origin in infancy or childhood. When more information becomes available and the pathogenesis of these diseases is better understood the risk factor campaign can be broadened to include the entire population. Also it is of vital importance to attempt to develop through research the profile in infancy and childhood of the individual who is prone to develop atherosclerosis, coronary artery disease or essential hypertension. Hopefully this knowledge may eventually lead to effective prophylactic programs against these dreaded diseases.

REFERENCES

1. Hargerty R, J Maroney M W and Nadas A S. Essential hypertension in infancy and childhood. *Am J Dis Child* 92:535 1956
2. Slater R, J Geiger D W, Azzonardi P and Webb H W. Hypertension in children. *Can Med Assoc J* 81:71 1959
3. Daeschner C W Jr. Evaluation of the child with arterial hypertension. *J Miss State Med Assoc* 1:535 1960
4. Rosenheim M L. Hypertension in childhood. *Proc R Soc Med* 54:1093 1961
5. Lorge J M H. Hypertension in children and adolescents. I. Cause and diagnostic studies. *J Pediatr* 74:331 1967
6. Tackuchi J. Etiology of juvenile hypertension. *Jap Circ J* 30:178 1966
7. Zinner S R, Levy P S and Hass E S. Familial aggregation of blood pressure in childhood. *New Engl J Med* 281:161 1971
8. Londe S, Bourgoigne J J, Robson A M and Goldring D. Hypertension in apparently normal children. *J Pediatr* 78:569 1971
9. Londe S. Blood pressure in children as determined under office conditions. *Clin Pediatr* 7:11 1966
10. Londe S. Blood pressure standards for normal children as determined under office conditions. *Clin Pediatr* 7:400 1968
11. Mat r A M, Dublin L I and Mark H H. The normal blood pressure range and its clinical implications. *JAMA* 143:464 1950
12. Freis E D. The pathogenesis of essential hypertension. In Cort J H, Feenl V, Heyl Z and Jirka J. editors. *Proceedings of the Prague symposium Prague 1960*. Prague State Medical Publishing House p 117
13. Hoofler S W. The pathogenesis of essential hypertension. In Cort J H, Feenl V, Heyl Z and Jirka J. editors. *Proceedings of the Prague*

ble causes of hypertension were performed on 33 individuals as outpatients. Because of the paucity of abnormal findings in this group 41 patients were more extensively investigated as inpatients in the Clinical Research Unit of St. Louis Children's Hospital.

Possible causes for hypertension were found in only 5 patients who had abnormal malities of the urinary tract. The presence of obesity in 53 per cent of the children and a family history of parental hypertension in 44 per cent, however, were significantly higher than in normotensive subjects. The systolic and/or diastolic pressures were still elevated in 65 per cent of 46 patients who were followed for 3 to 8 years.

The absence of an apparent cause for the hypertension in all but 5 of the patients, the high prevalence of obesity and of parental hypertension, and the persistence of elevated pressure in two thirds of the children followed for over 3 years, raises the question whether this type of juvenile hypertension is a prelude to essential hypertension in later life. Additional studies by other investigators and continued study of our patients into adulthood may help clarify this perplexing question.

Why has it been considered that hypertension in children is usually secondary? The reason may be the lack of a logical frame of reference for the practitioner taking blood pressures of children. Because of this, authors writing about juvenile hypertension have arbitrarily considered 135 to 140/85 to 90 mm Hg as the upper limit of normal. However, since these values are higher than the ninetieth percentile for children under the age of 10 years in our studies,^{9,10} younger children with moderately elevated blood pressures would have been excluded. Furthermore, whereas the patients in our study were asymptomatic children whose elevated pressures were incidental findings, the cases usually reported in the literature were hospitalized symptomatic and severely hypertensive children.

As previously reported for both adults and children,^{12,13} the blood pressures of our patients fell after they were in the hospital. Can it be that reliance on hospital blood pressure determinations alone may overlook children whose pressures may be mod-

erately elevated in day to day life? Perhaps normal ranges for hospitalized children should also be established.

Since intensive investigation revealed conditions possibly related to hypertension in only 7 per cent of our patients, extensive and expensive hospital studies are not indicated in this type of child. The following kind of outpatient study would seem reasonable: inquiry for family history of hypertension, complete physical examination, including lower extremity blood pressure determination, blood and urine examination, creatinine clearance determination, checks on serum potassium and urea nitrogen levels, and a rapid sequence intra-venous pyelogram.

Recent evidence indicates that the treatment of adults with long standing essential hypertension reduces the risks of complications.¹⁴ Should treatment, therefore, be started in asymptomatic children with hypertension of unexplained origin? Probably not, because the pathogenesis of essential hypertension is as yet unknown, and there is no evidence at this time that these hypertensive children will develop fixed hypertension in later life. Also, the anti-hypertensive drugs have well known undesirable side effects, and we question the wisdom of their use in growing children. Finally, there is no information available as to whether the institution of antihypertensive therapy in childhood hypertensives will prevent the progression of the disease. It is known that obesity is a contributing factor and there is suggestive evidence that excessive sodium intake¹⁵ may play a role. There is therefore justification for recommending weight reduction in the hypertensive child and probably some reduction in his dietary salt intake. These children should have annual physical examinations including funduscopic examinations and urinalysis. From the standpoint of prophylaxis, hypertensive parents should be appraised of the influence of heredity, obesity, and possibly of salt intake in essential hypertension. It should be stressed that all advice be offered without creating needless anxiety.

The youngest age at which we have been able to obtain reliable auscultatory blood pressure readings under office conditions

was 3 years. Since we have documented elevated pressure as early as 3 years it is highly probable that hypertension may begin at an even earlier age. The necessity for establishing reliable blood pressure standards from early infancy to 3 years of age is obvious. There are now instruments available for the measurement of blood pressure in infancy¹⁸ and it is hoped that pediatricians will make use of these new techniques. Once reliable standards are established for this age group the question of how early hypertension appears may be answered.

The much higher incidence of hypertension and cardiovascular disease among black adults than among white leads to the question of how early in life this difference appears. Unfortunately there were not enough black children in the population studied by us to answer this question. Rose¹⁹ who compared black and white tenth grade children found no difference. Whether this is true for younger children awaits further investigation.

Our observations point to broader horizons for preventive pediatrics. The importance of spotting an early tendency to hypertension needs no emphasis to the readers of this Journal. However the importance of careful routine blood pressure determinations does need emphasizing to the practitioner treating children. The implications from the public health standpoint are clear. Furthermore just as the routine tuberculin test in the young sometimes leads to uncovering adult tuberculosis so may the finding of hypertension in children lead to the uncovering of hypertension in parents who may not have had blood pressure determination for a long time.

The studies herein discussed also indicate the necessity of continuing extramural research on healthy populations as well as continuing research in medical centers which concern themselves mainly with sick people. Only by continued observations of healthy infants and children will we be able to pot minor but significant deviations from the normal which may affect longevity.

The educational campaign on the concept of risk factors in atherosclerosis and

coronary artery disease which has been mounted by the American Heart Association has been aimed exclusively at the adult population. It may well be that both these diseases as well as essential hypertension have their origin in infancy or childhood. When more information becomes available and the pathogenesis of these diseases is better understood the risk factor campaign can be broadened to include the entire population. Also it is of vital importance to attempt to develop through research the profile in infancy and childhood of the individual who is prone to develop atherosclerosis, coronary artery disease or essential hypertension. Hopefully this knowledge may eventually lead to effective prophylactic programs against these dreaded diseases.

REFERENCES

- 1 Hagerty P J, Maroney M W and Nadav A S. Essential hypertension in infancy and childhood. *Am J Dis Child* 9: 535 1959.
- 2 Slater R J, Geier D W, Azzopardi P and Webb B W. Hypertension in children. *Can. Med Assoc. J* 81 71 1959.
- 3 Daeschner C W Jr. Evaluation of the child with arterial hypertension. *J Miss State Med Assoc* 1 535 1960.
- 4 Rosenheim M L. Hypertension in childhood. *Proc R Soc Med* 54 1093 1961.
- 5 Longie J M H. Hypertension in children and adolescents. I. Causes and diagnostic studies. *J Pediatr* 74 331 1969.
- 6 Tackeuchi J. Etiology of juvenile hypertension. *Jap Circ J* 30 118 1966.
- 7 Zinner S H, Levy P S and Kass E H. Familial aggregation of blood pressure in childhood. *New Engl J Med* 281 461 1971.
- 8 Londe S, Bourgoignie J J, Robson A M and Goldberg D. Hypertension in apparently normal children. *J Pediatr* 78 569 1971.
- 9 Londe S. Blood pressure in children as determined under office conditions. *Clin. Pediatr* 5 71 1966.
- 10 Londe S. Blood pressure standards for normal children as determined under office conditions. *Clin Pediatr* 7 400 1968.
- 11 Master A M, Dublin L I and Marks H H. The normal blood pressure range and its clinical implications. *JAMA* 143:464 1950.
- 12 Freis E D. The pathogenesis of essential hypertension. In: Cort J H, Fencel V, Hejl Z and Jurka J, editors. *Proceedings of the Prague symposium*. Prague 1960. Prague State Medical Publishing House 112.
- 13 Hoobler S W. The pathogenesis of essential hypertension. In: Cort J H, Fencel V, Hejl Z and Jurka J, editors. *Proceedings of the Prague*

- symposium Prague 1960 Prague State Medical Publishing House p 314
- 14 Katcher A I Hypertension in adolescent children *Med Clin North Am* 18 1467 1964
- 15 Clayton G W and Hughes J G Variations in blood pressure in hospitalized children *J Pediatr* 40 462 1952
- 16 Freis E D Medical treatment of chronic hypertension *Mod Concepts Cardiovasc Dis* 10:17 1971
- 17 Guthrie H A Infant feeding practices—a predisposing factor in hypertension? *Am J Clin Nutr* 21 863 1965
- 18 Hernandez A Goldring D and Hartmann A F Jr Measurement of blood pressure by the Doppler ultrasonic technique (In pre-Pediatrics)
- 19 Rose C A study of blood pressure among Negro children *J Chronic Dis* 15 373 1962

Blood pressures of 'Kung bushmen in Northern Botswana

I S Truswell MB ChB MD MRCP
B M Kennelly MB ChB PhD MRCP
J D L Hansen MB ChB MD FRCP DCH
R B Lee* VA PhD

Cape Town and Johannesburg South Africa and Cambridge Mass

About a dozen groups of people in the world do not show the rise of blood pressure with increasing age that is the average pattern in developed countries. These groups have nearly all been found in remote parts of the world (Table 1). But the observations that can be made on these communities far from medical school laboratories are not only of anthropological interest they may also contribute to our understanding of the nature and cause of essential hypertension. The normotensive community we describe here has not been reported hitherto in the medical literature except for our preliminary communications^{1,2}

Subjects and methods

We report here some of our investigations among bushmen of the 'Kung tribe in northwestern Ngamiland Botswana near the Altai Hills. The 800 bushmen in this area have been kept isolated by a surrounding waterless zone 60 to 100 miles

wide.³ They live as independent a life as any bushman group in existence today. Many of them still live all the year round as hunter gatherers.⁴

I DeVore and R B Lee of the Department of Social Relations Harvard University set up a camp next to the bushman camp near the Dobe waterhole in 1963. Since then except for the period 1965-6 the Harvard group has had one to three anthropologists living in the area usually for periods of about 2 years. The resident scientists have learnt the 'Kung language got to know the people and each has studied a different aspect of bushman life taking pains however to disturb it as little as possible. Specialists have been brought to the camp from time to time for short visits which have been fruitful because the visitors have been able to base their studies on the resident scientists' personal knowledge and understanding of the bushmen.

The bushmen live in camps of 20 or more people the basis of which is an ex-

From the Department of Medicine, University of Cape Town, South Africa; the Department of Psychiatry, University of Cambridge, England; the Department of Medicine, University of Cape Town, South Africa; the Department of Social Relations, Harvard University, Cambridge, Mass. Accepted for publication August 16, 1972.
Revised manuscript received November 1, 1972.
Requests for reprints to: Dr. I. S. Truswell, Department of Medicine, University of Cape Town, P.O. Box 770, Cape Town 8000, South Africa.
*Present address: Department of Anthropology, Rutgers University, New Brunswick, N.J. 08903.

Table 1 Communities in which blood pressure does not rise with age

Ethnic or socio economic group	Geographical location	Study
1 Africans	Kivirondo Kenya	Donnison 1929
2 Africans	Eastern Province Uganda	Williams 1941
3 Ponape Islanders	1 Caroline Islands Micronesia	Murrill 1949
4 Iukupuk Islanders	N Cook Islands Polynesia	Murphy 1955 Hunter 1967 Prior et al 1968
5 Ethiopians	Ethiopia	ICNND 1958
6 Various communities	I Papua and E New Guinea	Whyte 1958 Maddocks 1965 1967
7 Lower socio economic group men— industrial and rural	Delhi India	Idumavati 1959
8 Bushmen	Central Kalahari Botswana	Kanner 1960
9 Aburung Islanders	Gilbert Islands Micronesia	Maddocks 1961
10 Carajas Indians	Amazon basin N Brazil	Iowenstein 1961
11 Simbura Rendille } nomads Turkana }	Northern Frontier Province Kenya	Shaper 1961 1967
12 Maasai tribesmen	Tanzania	Mann et al 1964
13 Orang Asli	West Malaysia	Burns Cox 1970

tended family group. Each camp is associated with a waterhole. Lee⁶ has found that about 70 per cent of food by weight is vegetable collected by the women. A variety of nuts, fruits, roots, bulbs and leaves are available varying with the season. The most important food is the nut of the mongongo (*marikettu*) tree (*Racodendron rautenensis*) because it is abundant, keeps well and is rich in protein and fat.⁷ Meat is provided by some of the men who hunt with poisoned arrows.

The bushmen have only a few basic possessions which they carry with them when they move; they are therefore able to travel light. Individuals move freely between camps and the camps move about five times a year. During and after the wet season (November to March) there are pans of seasonal water out in the bush so that the bushmen can camp beside them and collect food in the surrounding area. But as the pans dry up the bushmen return to the permanent waterholes at the end of the dry season; they have to walk increasing distances to find food. Some of the bushmen obtain milk occasionally from Bantu (Herero and Tswana) pastoralists who have settled in the area in the last 45 years. A few bushmen work for the Bantu as herdsmen part of the year. The bushmen have no

alcohol but they smoke tobacco. They have very little salt. There are no deposits of salt in the area and the principal means of obtaining salt is to walk to Tsumkwe 30 miles away in South West Africa where the Administration has established a settlement for the Kung bushmen on the South West African side of the border.

The medical team made 3 visits to the Ilarard camp; each trip included 10 days work in the field. The first visit was made in October, 1967 at the end of the dry season when it was hot and dry and food was scarce. The second visit was in April/May 1968 after the rains. During that visit it was warm in the day and cool at night; there were occasional pans of standing water in the area and some of the bushmen showed signs of malnutrition. The third visit was made in July 1969 halfway through the dry season. Though the nights were cold the days were sunny and quite warm out of the wind. There was adequate food.

The bushmen were seen in family groups. Babies, pregnant women, the sick and the aged were all included in our first two visits. A brief history was taken through an interpreter and each individual was examined with the subject lying down. At the third visit we examined only adults for

1 June 84
10 May 84

Table 11 Mean blood pressures of bushmen in age and sex subgroups

Age (years)	15-19	20-29	30-39	40-49	50-59	60-69	70-83	Total numbers
Men (n)	120/75 (3)	121/75 (16)	120/75 (19)	116/75 (17)	118/77 (14)	113/67 (6)	117/66 (4)	(79)
Women (n)	114/72 (5)	114/73 (17)	113/73 (13)	116/74 (17)	123/ 6 (9)	130/72 (8)	123/68 (4)	(73)
Both sexes (n)	117/73.5 (8)	119/74 (33)	116.5/74 (37)	116/74.5 (34)	120.5/74 (23)	121.5/69.5 (14)	120/67 (8)	(152)
Mean for both sexes	88.0	89.0	88.7	88.3	89.5	86.8	84.7	

$$D \text{ syst} + \frac{\text{by } 100 \times d}{3} \text{ i.e.}$$

whom we also recorded electrocardiograms (ECG's). The ages of the bushmen have been carefully worked out using rank ordering and relating this to known historical events in the neighborhood. The statistical technique for age determination was developed by Dr Nancy Howell Lee, the demographer on the Harvard expedition and now at the Office of Population Research, Princeton, N.J. The bushmen living within 10 miles of Dobe were brought to the base camp by truck for the examination. Any who were ill were treated. To examine the bushmen at the extreme east of the area (Nahopa and Goshu) and all those living south of the Aha Hill (Vat'vi and Vorigana) we took our equipment with us and drove to the bushman camps.

Blood pressures were measured with the same mercury sphygmomanometer (Brünnanometer) throughout, usually by Dr Trussell. They were taken in the right arm with a cuff measuring 13 by 24 cm. During the first two visits most of the subjects were examined on an improvised examination couch inside the medical tent where it was a little cooler than out in the sun. On the third visit the people were examined on a camp stretcher outside in the sun with the truck drawn up to provide shelter from the wind. Conditions were unhurried and we tried to help the subjects feel relaxed. Blood pressures were measured during the course of a full medical examination and the subject was lying down with his family waiting nearby.

Twenty-four hour urine specimens were

collected from 6 bushmen living at Dobe and from 2 controls (ourselves) in 1967 and from 4 of the same bushmen and from 3 controls in 1968. On each occasion the urines were collected on the eve of our return journey. Aliquots (preserved with iodine in 1967 and with oxalic acid in 1968) were carried back with us by jeep and plane in a cool box and frozen as soon as we arrived in Cape Town.

Urinary sodium and potassium were measured by flame photometry with lithium as internal standard and chloride was measured by potentiometric titration in an Aminco chloride titrator. Creatinine was measured with alkaline picric acid and nitrophenol by Kjeldahl.

Results

Blood pressures were measured in a total of 152 bushmen aged 15 to 83 years. The study group was composed of 79 men and 73 women. Measurements in 22 bushmen were taken on each of our 3 visits; another 22 subjects were measured on 2 of the 3 visits. The remaining 108 bushmen were examined only once. For each bushman we used all the available measurements to obtain a best estimate of blood pressure which was therefore based on 2 or 3 repeated measurements at different seasons in 14 of the subjects and on a single measurement in the rest (108 subjects). The individual blood pressure values were grouped by sex and decade and the mean values of the 14 subgroups are shown in Table II.

In male bushmen systolic and diastolic pressures both showed a slight but definite downward trend with increasing age throughout adult life. In the women the line joining decade mean systolic pressures rose by about 10 mm Hg to a higher step in the second half of life. But their diastolic pressures stayed the same until the two oldest age groups, in which there was a slight drop.

Combining the values for men and women (unweighted mean values in the third row of Table II), systolic pressures were about 3 mm higher in people over 49 years of age while diastolic pressures fell after the age of 59. Pulse pressures were 42 to 45 mm from ages 15 to 49 years and 52 to 53 mm from ages 60 to 83 years. These trends are illustrated in Fig 1, against the curve of London blood pressures taken by Hamilton and associates⁹ (1954) which is typical of Western developed communities. The mean blood pressures (diastolic + $\frac{1}{3}$ pulse pressure) for men and women combined condense all the results into a row of single figures at the bottom of Table II. They show a remarkable constancy despite increasing age.

In the 22 bushmen who were examined on all three visits the mean blood pressures were

October 1967	April May 1968	July 1969
117/73	126/75	111/64

The difference cannot be explained by observer variation, nearly all were taken by AST. The lower readings at the July (winter) visit were unexpected. On this occasion subjects were examined outside in the winter sunshine and it is possible that they were more relaxed than when they were examined on their own inside the doctors' tent on the two earlier visits.

Table III shows the arm circumferences of the bushmen, arranged by sex and age. The measurements were taken midway between the right elbow and shoulder in about half the subjects whose blood pressures were recorded. The arm circumferences were at the lower end of the range in Western adults.^{10,11} In both sexes they

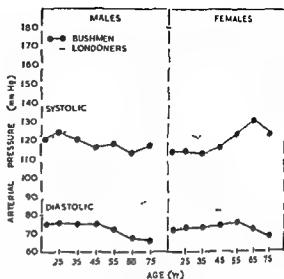


Fig 1 Bushmen's blood pressures with age compared with standard figures for a group from London (Hamilton and associates⁹)

were a little higher between 30 to 49 years of age and a little lower in the very young and the very old.

Almost all the bushmen examined were lean of delicate build and rather short. Taking all ages together the men averaged 48 Kg (106 lb) in weight (unclothed) and were 161 cm (5 ft 3 in) tall (without shoes). At this height the 'desirable' weight for small framed men is 53.5 to 57.2 Kg (118 to 126 lb) in the USA.¹² The women's mean height and weight were 150 cm (4 ft, 11 in) tall (without shoes) and 40 Kg (88 lb) (unclothed) compared with a 'desirable' weight range of 44.9 to 48.5 Kg (99 to 107 lb) for small framed women of the same height in the United States. Unfortunately these 'desirable' weights are quoted for people wearing indoor clothes which might weigh 1 to 2.25 Kg. The triceps skinfolds averaged 5.0 mm in the bushmen and 9.4 mm in the women.

To see if there were any changes in weight with age in the two sexes weight/height ratios (metric) are shown in Table IV together with ratios calculated from average US weights.¹² All bushman values were low and there was little change with age except below the age of 20 and over the age of 69 years. For comparison the weight/height index of young American men was 38.5 and it fell to 29.5 in the same men after 6 months semi-starvation with the loss of 25 per cent of their body

1 me 84
N mbe 3

Table III Arm circumference of bushmen in cm

Age (years)	15-19	20-29	30-39	40-49	50-59	60-69	70-81
Men	19.7 (3)	22.0 (11)	23.5 (11)	24.2 (6)	27.4 (1)	27.2 (1)	17.8 (3)
Women	18.4 (4)	20.2 (10)	21.4 (5)	21.4 (7)	19.0 (3)	21.8 (4)	16.6 (3)

Table IV Weight/height ratios for bushmen compared with ratios calculated from average U.S. weights*

Age (years)	15-19	20-29	30-39	40-49	50-59	60-69	70-83
Bushman							
Men	24.7	30.0	30.4	31.1	28.8	30.2	24.2
Women	24.0	27.5	26.4	27.0	27.1	26.1	24.7
Average U.S.							
Men	34.0	38.7	40.4	41.3	41.6	40.7	—
Women	31.6	33.4	36.0	38.1	38.9	39.3	—

* Ratios calculated from the following formula: $100 \times \frac{\text{weight (kg)}}{\text{height (m)}}^2$

1 N mbe of b m n each cell we g th saw aal T bl H
C lculat d f m shoe 5 ft 4 in. in h ght and w men l shoe 5 ft 1 in h ght

weight as observed in the Minnesota experiment¹¹

In the 24 hour urine specimens (Table V) the striking findings both in 1967 and 1968 were the low sodium and chloride content in the bushmen. Sodium and chloride excretions of 30 mEq per day each would correspond to an NaCl intake of only 2 cm per day. The creatinine excretions look rather low in one or two of the bushman urine specimens suggesting that the collections were incomplete. However the bushmen were smaller and weighed less than the controls. When the creatinines are expressed per kilogram of body weight the bushman creatinines come to 83 per cent of the controls in 1967 and 86 per cent in 1968. Potassium, nitrogen and magnesium excretions were not lower in the bushmen than in the controls.

Discussion

There have been two previous observations of blood pressures in other groups

of southern African bushmen. Bronte Stewart and colleagues¹⁴ mentioned mean values of 119/74 in men and mean values of 110/71 in women in northern South West Africa. Pressures were only taken in 44 subjects and old people were probably under-represented. Hamner and Lutz¹ measured blood pressures in 99 nomadic bushmen belonging to the Central Group of tribes living in the area south of Ghanzi, Botswana. The readings did not increase with age and none exceeded 140/90. Two complete bands of people were examined but ages could only be estimated by physical appearance.

We have confirmed these findings in a larger group of separate bushmen whose ages have been worked out with a fair degree of accuracy. There are different degrees to which populations can deviate from the standard Western blood pressure pattern exemplified by the curves for London presented in Fig. 2. Maddocks¹⁶ has introduced a useful classification. In the Type I pattern mean systolic pressure

Table V Mean values (and ranges) of 24 hour urinary sodium and other constituents in bushmen and controls

Subjects	Year	n	Creatinine (Gm/day)	Sodium (mEq/day)	Chloride (mEq/day)	Potassium (mEq/day)	Nitrogen (Gm/day)	Magnesium (mEq/day)
Bushmen	1967	6	0.81 (0.56-1.40)	31 (8-49)	30 (7-77)	70 (31-93)	10.4 (5.7-14.0)	4 (0.3-9.6)
	1968	4	0.98 (0.54-1.41)	29 (°-64)	36 (5-10)	107 (48-168)	10.6 (5.7-17.8)	
Controls	1967	2	1.36 (1.09-1.49)	212 (1.9-215)	173 (132-215)	68 (57-84)	8.7 (6.4-11.0)	3.9 (1.4-4.9)
	1968	3	1.42 (1.13-1.64)	147 (96-172)	121 (67-154)	61 (43-75)	11.4 (10.1-13.1)	

rises considerably with age and diastolic pressure rises moderately. In the Type II pattern, systolic pressure rises moderately but diastolic pressure does not rise. In the Type III pattern, systolic and diastolic pressures both stay at the same low level throughout life and in the Type IV pattern both systolic and diastolic blood pressures decline with advancing age. According to Maddock's classification the Kung bushman males have a Type IV pattern and the women a Type II pattern. When the two sexes and the diastolic and systolic pressures are combined the resulting mean blood pressures do not change with increasing age.

There are five possible explanations for the bushmen's immunity from hypertension: (1) low salt intake, (2) lack of obesity, (3) associated illnesses, (4) freedom from the stresses of civilization, and (5) high magnesium intakes. Taking them in reverse order, Verster¹⁷ speculated that the relatively high serum magnesiums found in some central African bushmen¹⁸ might be connected with their freedom from hypertension. However, these sera were not separated from red cells for about 2 days and neither Bernstein¹⁸ nor we (Table V) found high urinary magnesiums in bushmen.

There is no doubt that in some communities hypertension has appeared with "acculturation."¹⁹ But mental stress is only one of the changes that occur and it is the most difficult to quantify.²¹ Some isolated and peaceful communities have hypertension,²² although one would imagine they are not very stressful to live in.

Tropical splenomegaly²³ and chronic chest disease²⁴ have been associated with lower blood pressures than in the healthier

members of the same communities. A minority of the bushmen had splenomegaly but the spleens were usually not very large and appeared after the wet season, i.e., in April, 1968 when we found blood pressures to be rather higher than at our other visits. Some of the older bushmen showed evidence of chronic bronchitis but most of them appeared healthy on clinical examination. We would not think that chronic infections play more than a minor part in keeping blood pressures low. Maddocks and Vine²⁵ reached the same conclusion in New Guinea.

The bushmen have thin arms and small amounts of adipose tissue. Pickering, Roberts and Sowry¹⁰ calculated that to obtain the true direct blood pressure correction should be made for arm girth. According to the table in their article, 10 mm Hg should be added to the bushmen's direct systolic pressures and no correction should be made to the diastolic pressure.⁸ This would not explain the absence of hypertension with increasing age because the bushmen's arm circumference stayed about the same throughout life. More recent workers have found that the effect of arm girth per se is very small²¹ and that adiposity has a much closer association. The bushmen have unusually small amounts of adipose tissue and (Table IV) show no middle aged spread. Some of the other communities in Table I remain thin throughout life.

Lastly, our findings are consistent with Dahl's hypothesis⁸ that populations habitually consuming less than 5 Gm of salt a day are relatively free of hypertension. Some more recent between population comparisons²² are also in keeping with this hypothesis. Even if salt intake does not

determine which individuals become hypertensive within a developed community the bushmen appear to eat a low salt diet which provides little more sodium than was used to treat essential hypertension¹⁰ before oral diuretics became available

Summary

Blood pressures have been measured and sociological, anthropometric, medical and biochemical examinations have been made in an isolated group of !Kung bushmen in northern Botswana.

Blood pressures were taken in 152 bushmen of both sexes aged 15 to 83 years who were examined in family groups. Systolic and diastolic pressures declined with increasing age in the men. The women showed a small rise of systolic pressure after the menopause but their diastolic pressure decreased slightly with age. The mean blood pressure (diastolic + $\frac{1}{3}$ pulse pressure) for men and women combined thus remained the same throughout life.

Other communities whose blood pressures do not increase with age are reviewed. Of the possible explanations in the bushmen, a low salt intake and a lack of obesity appeared to be important with relative freedom from mental stress an additional inponderable factor.

We want to thank Professors I. DeVore, V. Schrire and J. E. Kench and Drs Nancy Howell, Lee Henry Harpending, Patricia Diaper and John E. Vellen for their help in this work.

REFERENCES

1. Truwell A S and Hansen J D L. Medical and nutritional studies of !Kung bushmen in north-west Botswana: a preliminary report. *S Afr Med J* 4: 1334 1968.
2. Truwell A S and Hansen J D L. Serum lipids in bushmen. *Lancet* 11: 83 1968.
3. Truwell A S and Hansen J D L. Winnebush P and Sellmeyer F. Nutritional status of adult bushmen in the Northern Kalahari Botswana. *S Afr Med J* 43: 1157 1969.
4. Thomas E M. The harmless people. London 1959. Secker & Warburg.
5. Lee R B. The subsistence ecology of !Kung bushmen. Ph.D. dissertation. Berkeley Calif 1965. University of California.
6. Lee R B. What hunters do for a living or how to make it on scarce resources. In Lee R B and DeVore I. *Man the Hunter*. Chicago 1968. Aldine Publishing Company, p 30.
7. Webber A S, Lee R B and Whitcomb M. The nutrient composition and dietary im-

- portance of some vegetable foods eaten by the !Kung bushmen. *S Afr Med J* 43: 1579 1969.
8. Kennelly B M, Truwell A S and Schrire V. A clinical and electrocardiographic study of !Kung bushmen. *Circulation* 40: Res Abstracts of the VI World Congress of Cardiology London 6-14 September 1970: 185.
9. Hamilton M, Pickering G W, Robert J A F and Sowry G S C. The aetiology of essential hypertension. 1. The arterial pressure in the general population. *Clin Sci* 13: 111 1954.
10. Pickering G W, Roberts J A F and Sowry G S C. The aetiology of essential hypertension. 3. The effect of correcting for arm circumference on the growth rate of arterial pressure with age. *Clin Sci* 17: 767 1954.
11. Karvonen M J, Telivuo L J and Järvinen E J. K. Sphygmomanometer cuff size and the accuracy of indirect measurement of blood pressure. *Am J Cardiol* 13: 688 1964.
12. Documenta Geigy Scientific Tables 6th Ed. Diem K, editor. Basel 1967. Geigy pp 673-674.
13. Keys A, Brozek J, Henschel A, Mickelson O and Taylor H. The biology of human starvation. Vol 1. Minneapolis 1950. University of Minnesota Press, p 146.
14. Bronte-Stewart B, Budtz-Olsen O F, Hickley J M and Brock J F. The health and nutritional status of the !Kung bushmen of South West Africa. *S Afr J Lab Clin Med* 6: 187 1960.
15. Hamner B and Lutz W P W. Blood pressure in bushmen of the Kalahari Desert. *Circulation* 22: 299 1960.
16. Maddocks J. Dietary factors in the genesis of hypertension. In Mills C F and Passmore R, editors. *Proceedings of the 6th International Congress of Nutrition*. Edinburgh 1964. E & S Livingston Ltd, p 137.
17. Verster F. Magnesium in die kardiovaskulere steel. *Geneeskunde* 3: 763 1961.
18. Bernstein F F. Blood electrolytes in a bushman group. *Proc Nutr Soc S Afr* 2: 56 1961.
19. Lowenstein F W. Blood pressure in relation to age and sex in the Tropics and Subtropics. A review of the literature and an investigation in two tribes of Brazil Indians. *Lancet* 1: 389 1961.
20. Cruz-Coke R, Etcheverry R and Nagel R. Influence of migration on blood pressure of Foster Islanders. *Lancet* 1: 97 1964.
21. Scotch V A and Geiger H J. The epidemiology of essential hypertension. II. Psychologic and sociocultural factors in etiology. *J Chronic Dis* 16: 1183 1963.
22. Hawthorne V M, Gills C R, Lottner A R, Calvert F R and Walker T J. Blood pressure in a Scottish island community. *Br Med J* 4: 651 1969.
23. Abrahams D G, Vele C A and Barnard B G. The systemic blood pressure in a rural West African community. *W Afr Med J* 9: 15 1960.
24. Miller D C, Spencer S S and White P D. Survey of cardiovascular disease among Afri-

Table V Mean values (and ranges) of 24 hour urinary sodium and other constituents in bushmen and controls

Subjects	Year	n	Creatinine (Gm/day)	Sodium (mEq/day)	Chloride (mEq/day)	Potassium (mEq/day)	Nitrogen (Gm/day)	Magnesium (mEq/day)
Bushman	1967	6	0.54 (0.56-1.40)	31 (8-45)	30 (7-77)	70 (31-93)	10.4 (5.7-14.9)	7.4 (6.3-9.6)
	1968	4	0.93 (0.54-1.41)	29 (°-64)	36 (5-70)	103 (45-168)	10.6 (5.5-17.5)	
Controls	1967	■	1.36 (1.09-1.47)	21° (179-245)	173 (13°-215)	68 (5°-84)	8.7 (6.4-11.0)	3.0° (1.4-4.7)
	1968	3	1.4° (1.23-1.64)	147 (96-177)	171 (6°-154)	61 (43-75)	11.4 (10.1-13.1)	

rises considerably with age and diastolic pressure rises moderately. In the Type II pattern, systolic pressure rises moderately but diastolic pressure does not rise. In the Type III pattern, systolic and diastolic pressures both stay at the same low level throughout life, and in the Type IV pattern both systolic and diastolic blood pressures decline with advancing age. According to Maddocks' classification the 'Kung bushman males have a Type IV pattern and the women a Type II pattern. When the two sexes and the diastolic and systolic pressures are combined the resulting mean blood pressures do not change with increasing age.

There are five possible explanations for the bushmen's immunity from hypertension: (1) low salt intake (2) lack of obesity (3) associated illnesses (4) freedom from the stresses of civilization and (5) high magnesium intakes. Taking them in reverse order Verster¹⁷ speculated that the relatively high serum magnesiums found in some central Kalahari bushmen¹⁸ might be connected with their freedom from hypertension. However these sera were not separated from red cells for about 2 days and neither Bernstein¹⁹ nor we (Table V) found high urinary magnesiums in bushmen.

There is no doubt that in some communities hypertension has appeared with acculturation.^{19, 20} But mental stress is only one of the changes that occur and it is the most difficult to quantify.²¹ Some isolated and peaceful communities have hypertension, although one would imagine they are not very stressful to live in.

Tropical splenomegaly^{22, 26} and chronic chest disease²⁴ have been associated with lower blood pressures than in the healthier

members of the same communities. A minority of the bushmen had splenomegaly but the spleens were usually not very large and appeared after the wet season, i.e., in April, 1968, when we found blood pressures to be rather higher than at our other visits. Some of the older bushmen showed evidence of chronic bronchitis but most of them appeared healthy on clinical examination. We would not think that chronic infections play more than a minor part in keeping blood pressures low. Maddocks and Vine⁶ reached the same conclusion in New Guinea.

The bushmen have thin arms and small amounts of adipose tissue. Pickering, Roberts, and Sowry¹⁰ calculated that to obtain the true direct blood pressure, correction should be made for arm girth. According to the table in their article 10 mm Hg should be added to the bushmen's direct systolic pressures and no correction should be made to the diastolic pressures.²⁵ This would not explain the absence of hypertension with increasing age because the bushmen's arm circumference stayed about the same throughout life. More recent workers have found that the effect of arm girth per se is very small^{11, 27} and that adiposity has a much closer association. The bushmen have unusually small amounts of adipose tissue and (Table IV) show no 'middle aged spread'. Some of the other communities in Table I remain thin throughout life.

Lastly, our findings are consistent with Dahl's hypothesis²³ that populations habitually consuming less than 5 Gm. of salt a day are relatively free of hypertension. Some more recent between population comparisons⁸ are also in keeping with this hypothesis. Even if salt intake does not

determine which individuals become hypertensive within a developed community the bushmen appear to eat a low salt diet which provides little more sodium than was used to treat essential hypertension²⁰ before oral diuretics became available

Summary

Blood pressures have been measured and sociological anthropometric medical and biochemical examinations have been made in an isolated group of *!Kung* bushmen in northern Botswana

Blood pressures were taken in 152 bushmen of both sexes aged 15 to 83 years who were examined in family groups. Systolic and diastolic pressures declined with increasing age in the men. The women showed a small rise of systolic pressure after the menopause but their diastolic pressure decreased slightly with age. The mean blood pressure (diastolic + 1/3 pulse pressure) for men and women combined thus remained the same throughout life.

Other communities whose blood pressures do not increase with age are reviewed. Of the possible explanations in the bushmen a low salt intake and a lack of obesity appeared to be important with relative freedom from mental stress an additional inponderable factor.

We want to thank Professors J. DeVore, V. Schrire and J. E. Kench and Drs. Nancy Howell, Lee Henry Harpending, Patricia Disper and John E. Ellen for their help in this work.

REFERENCES

1 Truwell A S and Hansen J D L Medical and nutritional studies of *!Kung* bushmen in north west Botswana a preliminary report *S Afr Med J* 42:1334 1968
2 Truwell A S and Hansen J D L Serum lipids in bushmen *Lancet* II 684 1968
3 Truwell A S Hansen J D L Wannenburg P and Sellmeyer E Nutritional status of adult bushmen in the Northern Kalahari Botswana *S Afr Med J* 43:1157 1969
4 Thomas H M The harmless people London 1959 Secker & Warburg
5 Lee R B The subsistence ecology of *!Kung* bushmen Ph.D. dissertation Berkeley Calif 1965 University of California
6 Lee P B What hunters do for a living or how to make out on scarce resources in Lee R B and DeVore I Man the Hunter Chicago 1968 Aldine Publishing Company p 30
7 Wehmeyer A S Lee R B and Whitman M The nutrient composition and dietary im-

portance of some vegetable foods eaten by the *!Kung* bushmen *S Afr Med J* 43:1579 1969
8 Kennelly M M Truwell A S and Schrire V A clinical and electrocardiographic study of *!Kung* bushmen Cardiovasc Res Abstracts of the VI World Congress of Cardiology London 6-17 September 1970 p 185
9 Hamilton M Pickering G W Robert J A F and Sowry G S C The aetiology of essential hypertension 1 The arterial pressure in the general population *Clin Sci* 13:11 1954
10 Pickering G W Roberts J A F and Sowry G S C The aetiology of essential hypertension 3 The effect of correcting for arm circumference on the growth rate of arterial pressure with age *Clin Sci* 13:767 1954
11 Karvonen M J Tehtuo L J and Jarvinen E J K Sphygmomanometer cuff size and the accuracy of indirect measurement of blood pressure *Am J Cardiol* 13:688 1964
12 Documenta Geigy Scientific Tables 6th Ed Diem K editor Basel 1967 Geigy pp 673 674
13 Keys A Brozek J Henschel A Mickelson O and Taylor H L The biology of human starvation Vol I Minneapolis 1950 University of Minnesota Press p 146
14 Bronte-Stewart B Budtz-Olsen O H Hickley J M and Brock J F The health and nutritional status of the *!Kung* bushmen of South West Africa *S Afr J Lab Clin Med* 6:187 1960
15 Kaminer B and Lutz W P W Blood pressure in bushmen of the Kalahari Desert *Circulation* 22:289 1960
16 Maddocks J Dietary factors in the genesis of hypertension in Mill C F and Passmore R editors Proceedings of the 6th International Congress of Nutrition Edinburgh 1964 E & S Livingston Ltd p 137
17 Verster F Magnesium in die kardiovaskulere aetioel *Geneeskunde* 3:263 1961
18 Bernstein P F Blood electrolytes in a bushman group *Proc Nutr Soc S Afr* 2:36 1961
19 Lowenstein F W Blood pressure in relation to age and sex in the Tropics and Subtropics A review of the literature and an investigation in two tribes of Brazil Indians *Lancet* I:389 1961
20 Cruz Coke R Etcheverry R and Vazir R Influence of migration on blood pressure of Easter Islanders *Lancet* I:97 1964
21 Scotch V A and Geier H J The epidemiology of essential hypertension II Psychological and sociocultural factors in etiology *J Chronic Dis* 16:1183 1961
22 Hawthorne V M, Galis C R, Lerner A R, Calvert F R and Walker T J. Blood pressure in a South African community *Br Med J* 4:511 1969
23 Abraham D G, Lee C L and Birtani P G The systolic blood pressure in a South African community *Br Med J* 9:41 1969
24 Merz D C, Cline G S and Zia J P Blood pressure in the *!Kung* bushmen in

- crans in the vicinity of the Albert Schweitzer Hospital in 1960 *Am J Cardiol* 10:432 1962
- 25 Burns Cox C J and Wiclean J D Splenomegaly and blood pressure in an Orang Asli community in West Malaysia *Am HEART J* 80:718 1970
 - 26 Maddocks I and Vine A P The influence of chronic infection on blood pressure in New Guinea males *Lancet* II 262 1966
 - 27 Kannel W B Brand N Skinner J J Jr Dawber T R and McNamara J M The relation of adiposity to blood pressure and development of hypertension *Ann Intern Med* 67:48 1967
 - 28 Dahl I K Possible role of chronic excess salt consumption in the pathogenesis of essential hypertension *Am J Cardiol* 8:571 1961
 - 29 Evans J G and Rose G Hypertension *Br Med Bull* 27:37 1971
 - 30 Chapman C H and Gibbons T B The diet and hypertension A review *Medicine* 29:29 1950

ADDITIONAL REFERENCES FOR TABLE I

- Donnison C P Blood pressure in the African native *Lancet* I 6 1929
- Williams A W The blood pressure of Africans *E Afr Med J* 18:109 1941
- Murrill R I A blood pressure study of the natives of Ponape Island Eastern Carolines *Hum Biol* 21:47 1949
- Murphy W Some observations on blood pressures in humid tropics *N Z Med J* 54:64 1955
- Hunter J D Diet body build blood pressure and serum cholesterol levels in coconut eating Polynesians *Fed Proc* 21(4) part 2:36 1962
- Prior I A M Evans J G Harvey H P B Davidson F and Lindley M Sodium intake and blood pressure in two Polynesian populations *New Engl J Med* 279:515 1968
- Ethiopia 1958 Nutrition Survey A Report by the Interdepartmental Committee on Nutrition for National Defense (ICNND) Washington D C September 1959 U S Government Printing Office
- Whyte H M Body fat and blood pressure of natives in New Guinea Reflections on essential hypertension *Australas Ann Med* 7:136 1958
- Maddocks I and Rovin L A New Guinea population in which blood pressure appears to fall as advances Papua New Guinea *Med J* 117 1965
- Maddocks I Blood pressure in Melanesians *Med J Aust* 1:1123 1967
- Pidmavati S and Gupta S Blood pressure studies in rural and urban groups in Delhi *Circulation* 19:395 1959
- Maddocks I Possible absence of essential hypertension in two complete Pacific Island populations *Lancet* II 396 1961
- Shaper A G Williams A W and Spencer P Blood pressure and body build in an African tribe living on a diet of milk and meat *E Afr Med J* 38:569 1961
- Shaper A G Blood pressure studies in East Africa in Stamler J Strimling R and Pullman T N editors The epidemiology of hypertension New York and London 1967 Grune & Stratton Inc p 139
- Mann G V Shaffer R D Anderson K S and Sindsted H H Cardiovascular disease in the Masai *J Atheroscler Res* 4:289 1964

Cardiomyopathy without cardiomegaly in alcoholics

Sankaran K. Asokan MD

Martin J. Frank MD

A. Calhoun Witham MD

Augusta Ga

Clinical and experimental evidence in recent years has prompted physicians to recognize the entity of alcoholic cardiomyopathy with increasing frequency.¹⁻⁵ There is evidence that acute administration of alcohol to normal humans produces myocardial cellular damage as evidenced by loss of intracellular constituents such as potassium phosphates and enzymes with associated impairment of hemodynamic function.⁶⁻⁸ Despite the wide prevalence of alcoholism in this country cardiac symptoms in an alcoholic patient have often been ignored unless obvious clinical electrocardiographic (ECG) or radiologic evidence of cardiomegaly or arrhythmias is present. Clinicians often wait until cardiac enlargement is obvious prior to entertaining the possibility of myocardial involvement. We have attempted to define an earlier stage of this syndrome and we therefore studied a group of alcoholic patients with mild functional impairment who otherwise presented with no increase in cardiothoracic ratio on chest x-ray and who had normal ECG's.

Materials and methods

Hemodynamic studies were performed in nine patients with a history of alcoholism

(moonshine drinking) of 5 to 25 years duration. They were selected from those who had presented to the outpatient clinic because of cardiac symptoms which could not readily be explained. Others had non cardiovascular ailments such as dermatological problems with no evidence of systemic involvement. There was no evidence of gross nutritional deficiency or anemia (hematocrit 45 ± 2) in these patients. Further all patients were studied after approximately three weeks of abstinence from alcohol while ingesting a regular hospital diet.

No patient had a history of delirium tremens or required sedatives or tranquilizers. Abnormal cardiovascular physical findings such as cyanosis, persistent splitting of S₂, abnormal parasternal lifts or apical thrusts were not present. Chronic lung disease was excluded clinically and also when it was indicated with pulmonary function tests when chest x-ray suggested minor parenchymal abnormalities or the presence of infiltrates. Liver and kidney function studies including Bromsulphalein and creatinine clearance were normal in all patients. Retinal vessels were normal. There were no histories suggesting recent viral illness. No patient had visited South

From the Medical College of Georgia, Augusta, Ga.

Supported in part by United States Public Health Service grant HE-42494 and National Institutes of Health grant RR-61-09.

Received for publication May 20, 1972.

Reprint requests to S. K. Asokan, MD, Medical College of Georgia, 1439 Governor's Office Building, Augusta, Ga. 30901.



Fig 1 Chest x ray of patient No 3 (W L)



Fig 2 Chest x ray of patient No 1 (N R)

America or other areas where Chagas disease is endemic.

Presenting symptoms in these patients were of a mild degree. Five had fatigue, four had dyspnea on exertion, and four experienced nonspecific chest pain. Physical examination revealed the presence of third heart sounds in four patients and fourth heart sounds in five patients. Abnormal cardiac function was suspected in the asymptomatic because of the presence of findings such as a third or fourth heart sound. Although there were no clear cut indications for diagnostic catheterization, the majority of these patients had volunteered for another study⁹ from this laboratory. In some patients (eg Nos 5 and 9) no cardiac dysfunction was expected on clinical grounds. In these and the others, the compelling reason for investigating these patients was the need to demonstrate whether a history of alcoholism alone is enough to anticipate abnormal cardiac function.

All patients had standard cardiac series¹⁰ with barium filled esophagus in four views. Cardiac silhouette, chamber size, pulmonary vascularity, etc were assessed to rule out lesions suggesting either congenital or acquired diseases such as shunts and valvular stenosis. All but one

patient had normal cardiothoracic ratios (Table I, Figs 1 and 2). Because of their ages (mean age 41 ± 2 yr) a relatively low prevalence of coronary heart disease was expected. Further, no history suggestive of coronary artery disease was obtained, and standard twelve lead electrocardiography and exercise testing gave no evidence for it. Nevertheless, those with chest pains, although atypical for angina pectoris, underwent selective coronary arteriography (Table I).

Right and left heart catheterization was performed under mild barbiturate sedation. The maximal rate of left ventricular pressure rise (MRPR) was recorded with an RC differentiating unit available in the multi channel recorder (Electronics for Medicine DR8). Catheters (60 cm 7.1 NIH) were of the shortest length with maximum diameter and were directly attached to the Statham strain gauges. Comparison of the conventional fluid filled catheter manometer system with a Statham SF1 catheter tip transducer has revealed that the former is linear up to dp/dt maximum of 2 500 mm Hg per second and exhibits a small (5 per cent) overestimate between 2 500 and 3 000 mm Hg per second.¹⁰

Further control data (Fig 5) were ob-

Table 1 Descriptive data in nine alcoholic patients with normal cardiothoracic ratios

Patient	Age (yr)	BSA (M ²)	LVHC†	CTR‡	Coronary arteriogram§
1 N K	46	1.87	1 A	0.45	—
2 D S	48	1.86	2 B	0.53	—
3 W L	39	1.87	2 C	0.46	✓
4 W C	37	1.67	2 C	0.44	—
5 H S	47	1.77	1 A	0.43	✓
6 I T	36	1.64	2 B	0.45	✓
7 W I	57	2.30	1 A	0.48	✓
8 I H	49	1.87	2 C	0.47	✓
9 H J St	37	1.67	1 A	0.46	✓
Mean	47	1.83		.46	
Standard error	2.3	0.07		.00	

BSA = Body surface area.

†LVHC = Left ventricular heart index.

‡CTR = Cardiothoracic ratio.

§C = coronary arteriogram.

A = aortic arteriogram.

tained in the same fashion by the same personnel. Cardiac outputs and left ventricular volumes were measured in duplicate using the indicator dilution method.¹¹ Significant shunts were also ruled out in this fashion. The presence of valvular regurgitation was essentially ruled out by dye dilution techniques and when indicated by angiography. Pericardial disease was excluded clinically and also at catheterization.^{12,13}

An index of contractility¹⁴ was employed to examine left ventricular performance. Briefly, this index is expressed as $\text{MRIR} \times \text{r} / \text{r}_0$. MRIR represents the maximum rate of left ventricular pressure rise. r_0 the maximum isovolumetric pressure, and r represents the circumferential fiber length of the left ventricle which helps to normalize the index for hearts of different sizes. Adjustments in the fiber length r were calculated assuming that the left ventricle was a sphere at the end of the systolic isovolumetric period, deriving the radius (r) from the end diastolic volume measured by indicator dilution. MRPK and r_0 (aortic diastolic pressure) were obtained simultaneously by means of two catheter systems, one in the left ventricle and the other in the aortic root. Estimates of LV volumes were done in duplicate within five minutes of the appropriate pressure recordings. Contractility indices obtained in this fashion were

compared with normals from this laboratory.¹⁴

Results

A summary of the hemodynamic data is shown in Tables I and II. The mean cardiac output was 2.56 ± 0.21 L. per minute per mole, which is significantly lower ($p < 0.05$) than expected for patients of this age group (3.19 ± 0.29 L. per minute per mole).¹ The left ventricular end-diastolic volume was normal in 7 out of 9 patients; in one patient it was slightly increased and in the other it was moderately increased. Left ventricular end diastolic pressures were elevated in all but two patients. It is noteworthy that two patients who were asymptomatic had decreased cardiac indices and elevated left ventricular end-diastolic pressures (patients Nos. 1 and 5). In patients whose coronary arteries were selectively opacified (Table I) no angiographic abnormalities were detected (e.g. Figs 3 and 4, patient No. 6). The calculated left ventricular contractility index was 0.67 ± 0.05 as compared to a normal of 1.27 ± 0.09 in our laboratory, a significant difference (Fig. 5).

Discussion

The growing number of alcoholic subjects with myocardial disease in the absence of a readily definable nutritional deficiency has increased acceptance of the concept that

Table II Hemodynamic data in nine alcoholic patients with normal cardiothoracic ratios

Patient no	Ra* (mm Hg)	RVLD (mm Hg)	RVS (mm Hg)	PAS (mm Hg)	PAD (mm Hg)	PAM (mm Hg)	CI (L/M ²)
1	4	10	35	35	10	21	1.97
2	8	12	35	35	12	22	2.35
3	5	10	38	38	15	22	3.07
4	4	4	40	40	11	21	1.63
5	5	5	29	29	8	17	2.27
6	3	9	24	24	9	16	2.14
7	5	5	28	28	10	18	2.84
8	5	14	38	38	21	26	3.67
9	11	19	32	32	19	24	3.2
Mean	5.5	9.7	33.2	32.3	12.7	20.7	2.56
Standard error	0.8	1.6	1.7	1.7	1.5	1.09	0.21

* Abbreviations: Ra = right atrium; RVLD = right ventricular end diastolic pressure; RVS = right ventricular systolic pressure; PAS = index; SVI = stroke volume index; EDVI = end diastolic volume index; MLR = maximal rate of left ventricular pressure rise; FF = aortic diastolic pressure.



Fig. 3 Selective coronary angiogram of the right coronary artery of patient No. 6 (F.T.). The vessel is normal in caliber and distribution.



Fig. 4 Selective coronary angiogram of the left coronary artery of patient No. 6 (F.T.). The vessel is normal in caliber and distribution.

alcohol itself is able to produce chronic functional myocardial impairment. However much of the published work on the clinical recognition of alcoholic cardiomyopathy^{2,4} stresses that cardiac enlargement is a prerequisite for its diagnosis. The majority of alcoholic patients with enlarged hearts, arrhythmias and recurrent heart failure have a poor prognosis. The need to recognize this entity prior to the development of severe and irreversible myocardial damage is obvious. Moreover many patients with normal ECGs and no

apparent cardiac enlargement are often suspected to be neurotic and their symptoms labelled "functional." While this may be true in some the present data indicate that this is not necessarily so. The cardiac outputs were significantly lower than predicted for patients of this age group.¹ The abnormally high mean left ventricular end diastolic pressures in this group in the presence of normal mean left ventricular end diastolic volume reflect a significant reduction in compliance of this chamber. A large end diastolic volume was obtained for

SVI (l/M)	EDVI (l/M ²)	VRPR (mm Hg/sec)	FF	CoI	LVS (mm Hg)	LAFD (mm Hg)	LVD (mm Hg)
26	67	933	0.41	0.64	112	13	74
39	108	1150	0.36	0.55	165	15	97
49	140	935	0.34	0.50	131	14	77
28	60	1164	0.46	0.63	165	15	98
35	64	1589	0.53	0.99	148	17	85
75	38	1041	0.44	0.58	148	10	99
41	83	1300	0.52	0.71	108	11	87
37	61	1360	0.67	0.89	174	28	81
38	83	1077	0.46	0.60	130	18	85
35	80	1166	0.46	0.67	137	16	85
1	9	77	0.07	0.05	6	17	2

SVI = stroke volume index; EDVI = end-diastolic volume index; VRPR = ventricular pressure rate; FF = fractional flow; CoI = cardiac output; LVS = left ventricular systolic pressure; LAFD = left atrial end-diastolic pressure; LVD = left ventricular end-diastolic pressure.

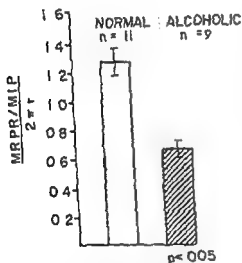


Fig. 3 Left ventricular contractility index for normal and patient with alcoholic cardiomyopathy

patient No. 3 in the face of a normal cardiothoracic ratio. This x-ray measurement is of course an insensitive method of predicting chamber volumes. We have also demonstrated evidence of decreased left ventricular function and depressed contractility in these patients even in the absence of ECG abnormalities or obvious radiological changes. Early recognition of this entity appears important in order to attempt timely rehabilitation. Although cardiac catheterization may not be clearly indicated in the majority evaluation of cardiac

performance at an early stage of the disease seems desirable. Noninvasive techniques of measuring cardiac performance such as measurement of systolic time intervals^{18,17} echocardiography¹⁸ and exercise stress testing may be useful in the initial assessment and follow up. With this in view we are at present assessing the value of serial measurement of systolic time intervals and exercise stress testing in detecting left ventricular functional impairment in alcoholic patients.

Summary

For obvious reasons it is important to recognize alcoholic cardiomyopathy early in its natural history. Hemodynamic studies were performed in nine patients with normal ECGs and normal cardiothoracic ratios on chest x-rays. Findings were elevated mean LV end-diastolic pressure, low mean cardiac output and depressed myocardial contractility. Thus true functional cardiac impairment may exist in these patients even prior to the development of abnormal clinical parameters such as cardiomegaly.

REFERENCES

1. Burch C E and Giles T D. Alcoholic cardiomyopathy. *Am J Med* 50:141 1971.
2. Burch C E and Wolff J J. Cardiac insufficiency in chronic alcoholism. *Am J Cardiol* 6:64 1960.
3. Burch C E and DePaquale N P. Alcoholic cardiomyopathy. *Am J Cardiol* 23:723 1969.

- 4 Wendt V I, Wu C, Valcon K, Doty C and Bing K. Hemodynamic and metabolic effects of chronic alcoholism in man. *Am J Cardiol* 15:175 1965
- 5 Regan I J, Levinson C F and Oldewurtel H A. Ventricular function in non-cardiacs with fatty liver. Role of ethanol in the production of cardiomyopathy. *J Clin Invest* 18:397 1969
- 6 Regan I J, Korovenidis C, Moschos C B, Oldewurtel H A, Lehan I H and Hellenis H K. Acute metabolic and hemodynamic responses of the left ventricle to alcohol. *J Clin Invest* 45:710 1966
- 7 Burch C F and Walsh J J. Cardiac enlargement due to myocardial degeneration of unknown cause. *JAMA* 172:207 1960
- 8 Regan I J, Levinson C F, Frank M J, Asokan S K and Moschos C B. The role of ethanol in left ventricular failure. *Circulation* 35(Suppl II):118 1967
- 9 Asokan S K and Frank M J. Improved cardiac performance in alcoholic cardiomyopathy after chelation. Presented at American Heart Association meeting Nov 11 1971. *Circulation* 44(Suppl II):40 1971
- 10 Weiner I, Dawes G I M and Cox J W. Left ventricular hemodynamics in exercise-induced angina pectoris. *Circulation* 38:240 1968
- 11 Levinson G F, Frank M J, Nadimi M and Brunstein M. Studies of cardiopulmonary blood volume. Measurement of left ventricular volume by dye dilution. *Circulation* 3, 1018 1967
- 12 Burch C F and Phillips J H. Methods in the diagnostic differentiation of myocardial dilatation from pericardial effusion. *Am Heart J* 64:266 1967
- 13 Limzey H W, Slater S, Elliot P and Elliot K S. The differential diagnosis of restrictive cardiomyopathy and chronic constrictive pericarditis without catheterization. Value of coronary arteriography. *Am J Cardiol* 25:635 1970
- 14 Frank M J and Levinson G F. An index of contractile state of the myocardium in man. *J Clin Invest* 47:1615 1968
- 15 Brandfonbrener M, Lindowne M and Shock N W. Changes in cardiac output with age. *Circulation* 12:531 1955
- 16 Weisler A M, Harris W S and Schoenfeld C D. Bedside techniques for the evaluation of ventricular function in man. *Am J Cardiol* 21:577 1969
- 17 Martin C F, Shaver J A, Thompson M F, Keddy I S and Leonard J F. Direct correlation of external systolic time intervals with interval indices of left ventricular function in man. *Circulation* 44:119 1971
- 18 Fortum N J, Hood W P Jr, Sherman M E and Cruickshank I. Determination of left ventricular volumes by ultrasound. *Circulation* 44:575 1971

Rules for the diagnosis of visceral situs, truncoconal morphologies, and ventricular inversions

Maria I. de la Cruz M.D.*

Bernardo Nadal Cinard M.D.**

Mexico City, Mexico

At the present time there is great confusion of concepts with respect to visceral situs^{1,6} the positions of the heart^{2,3,7,10} ventricular inversions^{2,11} and the truncoconal morphologies^{2,12} all of which has led to the creation of a vast nomenclature most of which is not correct.^{1,3,11,12,14,15} It is our belief that on the basis of embryologic facts^{16,17} the basic rules may be established and these will always apply. They are most useful for the anatomic and radiologic diagnosis of these entities both in their simple forms as well as in the complex varieties when they are associated with malformations of the atrioventricular canal such as persistence of the common atrioventricular canal, double inlet of the ventricles and atresia of the atrioventricular orifices.

Diagnosis of the visceral situs

A visceral situs is the position and the reciprocal spatial relation of the viscera within a system of symmetry.

There are two main types of situs: solitus and inversus. Although heterotaxias constitute a visceral situs, they will not be stud-

ied in this paper because due to their anatomic and embryologic features they do not conform to the rules which apply to situs solitus and situs inversus. The diagnosis of a situs is made by determining the position of those internal organs which do not change their position in space in an isolated fashion but rather remain permanently related to the type of situs of which they are part. Furthermore, they show features which permit the identification of the right and left structures.

The abdominal viscera which should be selected for the diagnosis of a situs is the liver, since it has the features previously mentioned while the stomach, the intestine and the spleen may change their spatial position independently of the situs of which they form part due to isolated malformations and malrotations of these organs.

The atria are the only chambers of the heart which serve the purpose of diagnosing a given situs because they do not vary their position independently of the situs and because the anatomical features of the right atrium are different from those of the left

From the Department of Embryology, Faculty of Medicine, National University of Mexico, Mexico City, D.F.

Received for publication November 25, 1971.

Reprints requested to: Maria I. de la Cruz, Chief, Department of Embryology, Faculty of Medicine, National University of Mexico, A.P. 703, Interoceanic Highway 300, Mexico City, D.F.

*Chief, Department of Embryology, Faculty of Medicine, National University of Mexico, A.P. 703, Interoceanic Highway 300, Mexico City, D.F.

**Chief of Residency, Faculty of Medicine, National University of Mexico, A.P. 703, Interoceanic Highway 300, Mexico City, D.F.

atrium and this permits their differentiation. The anatomically right atrium* has internal structures which identify it and it always receives the suprahepatic portion of the inferior vena cava, its atrial appendage is triangular with smooth borders while the anatomically left atrium has a specific internal architecture and possesses a smaller appendage than that of the right atrium, it exhibits a narrow neck at its base and its edges are irregular.

The superior vena cava is not a structure by which the diagnosis of an anatomically right atrium can be made. This is because this structure originates from the system of the anterior cardinal veins and the common cardinal veins, which are bilateral and asymmetric vessels in the embryo which may develop (1) normally persisting as the superior vena cava which drains into the anatomically right atrium while the opposite vein disappears, or (2) abnormally, persisting as both superior venae cavae or in the disappearance of the superior vena cava which normally drains into the anatomically right atrium while the opposite superior vena cava may drain directly into the anatomically left atrium or through the coronary sinus into the anatomical right atrium. The pulmonary veins are not useful to identify the anatomical left atrium either due to the fact that there may be a total anomalous pulmonary venous connection.

The diagnosis of a situs is made by locating the spatial position of the major lobe of the liver and the suprahepatic portion of the inferior vena cava together with the anatomical right atrium (hepatocaval atrial concordance). The radiological diagnosis of the anatomical right atrium is made by locating the suprahepatic portion of the inferior vena cava (Figs 1 to 5).

There is no such thing as atrial inversion because the position of the atria is fixed for each situs and therefore these chambers

are the cardiac structures which determine the situs.¹⁹ On the contrary there are two types of atrioventricular relations for each situs (Fig 1, B and C and Fig 2, B and C), depending on the concordant or discordant position of the ventricles with respect to the situs¹⁹ (Figs 3, 4, and 5).

The diagnosis of visceral situs solitus is established when the major lobe of the liver, the suprahepatic portion of the inferior vena cava, and the anatomically right atrium are placed on the right side independently of the position of the remaining viscera (Figs 1A, 3A and B, 4A and B, and 5A and B).

The diagnosis of visceral situs inversus is established when the major lobe of the liver, the suprahepatic portion of the inferior vena cava, and the anatomically right atrium are placed on the left side constituting therefore a mirror image of situs solitus (Figs 2A, 3C and D, and 4C and D).

The direction of the cardiac apex may have three distinct positions for each visceral situs: left sided apex, middle-placed position of the apex, or right sided apex. The nomenclature for the right or left position of the apex relates its direction with the visceral situs.²⁰ A normally placed heart is one in which the cardiac apex is directed to the left in a situs solitus (Fig 1J). The same direction of the cardiac apex in a heart which forms part of a situs inversus is designated as levoversion or heterocardia (Fig 2L).

The heart with a right sided apex in a situs solitus is best designated as dextroversion (Fig 1L) while that heart with an apex to the right in a situs inversus is best designated as mirror image dextrocardia (Fig 2J). The medial position of the cardiac apex is called mesocardia independently of the visceral situs of which it forms part (Figs 1K and 2K).

Diagnosis of truncal and morphologies

The truncus of the embryonic heart gives origin to the ascending aorta and the trunk of the pulmonary artery and its conus forms the infundibulum of the right and of the left ventricles.²¹ The study of the different truncal morphologies should be done in the following order: (1) one should specify

The anatomically right atrium is characterized by the presence of the crista terminalis which separates the smooth (non) portion from the pectinate muscle. The latter begins in the crista and directs the muscles to the apex of the atrial appendage. The anatomically left atrium has a smooth atrial appendage and a fine network of pectinate muscles.

When the truncus of the embryonic heart gives origin to the ascending aorta and the trunk of the pulmonary artery and its conus forms the infundibulum of the right and of the left ventricles, the study of the different truncal morphologies should be done in the following order: (1) one should specify

<p>VISCEA CONCORDANCE (C9, 310, 1)</p>		
<p>POSITION OF THE VENTRICLES (V9, 200, 1)</p>	<p>WITHOUT VENTRICULAR INVERSION</p>	<p>WITH VENTRICULAR INVERSION</p>
<p>TRUNCOCARDIAL MORPHOLOGY (V9, 200, 2)</p>		
<p>POSITION OF THE APEX (V9, 200, 3)</p>		

Fig. 1 Dagrams representing the typical atrial position in situs solitus, the atrioventricular relations, that of the great arteries with each other and those of the great arteries with the ventricles. The different directions of the cardiac apex are depicted. RA = anatomically right atrium, LA = anatomically left atrium, IVC = inferior vena cava, RV = anatomically right ventricle, LV = anatomically left ventricle, *ao* = aorta, PA = pulmonary artery, CT = common trunk.

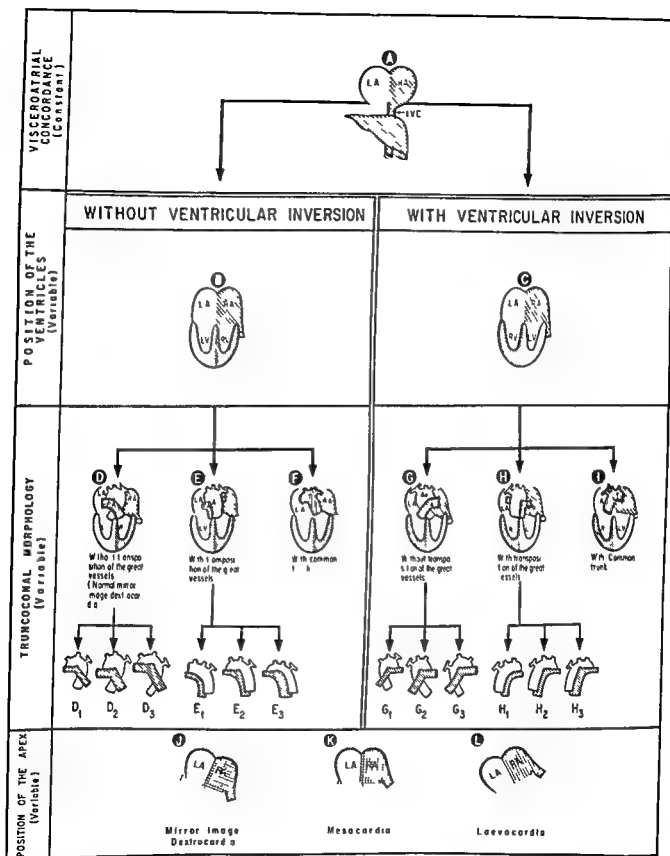
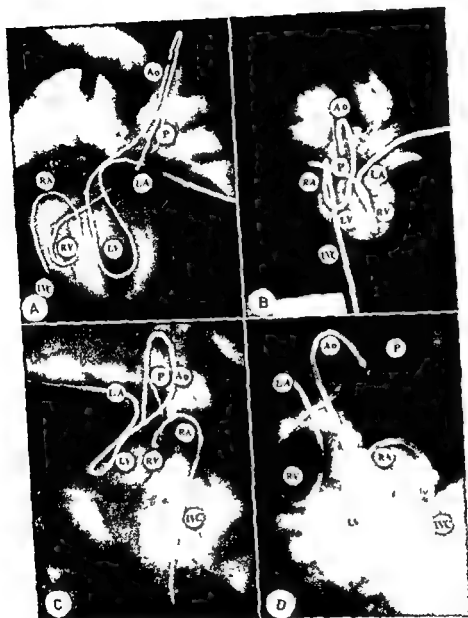


Fig. 2. Diagrams representing the characteristic atrial position in situs inversus, the atrioventricular relation, the position of the great arteries with each other and those of the great arteries with the ventricle. The different directions of the cardiac apex are depicted. *RI* = anatomically right atrium; *LI* = anatomically left atrium; *IVC* = inferior vena cava; *RV* = anatomically right ventricle; *LV* = anatomically left ventricle; *AO* = aorta; *PA* = pulmonary artery; *CT* = common trunk.



F 3 A through D Postmortem radiological studies with catheters placed in the cardiac chambers and the great arteries. Frontal view. Identification of the ventricular cavities by means of the spatial relation of the two great arteries between themselves. Panels A-D correspond to hearts with great arteries crossing each other (without transposition of the great arteries) in place. **A** Normal heart in situs solitus. **B** Ventricular inversion in situs solitus without transposition of the great arteries. **C** Normal heart in situs inversus (mirror image dextrocardia). **D** Ventricular inversion in situs inversus without transposition of the great arteries (mirror image dextrocardia). Note that in every case the pulmonary artery (P) crosses the aorta (Ao) ventrally, which means that there is no transposition of the great arteries. In Panel A and D the catheter placed in the pulmonary artery is directed from right to the left, indicating that the anatomically right ventricle (RV) is placed on the right. In Panels B and C the catheter in the pulmonary artery is directed from left to right, pointing out that the anatomically right ventricle is placed on the left. The portion of the catheter bearing the letters IVC shows that the inferior vena cava enters the anatomically right atrium (RA) (sign of situs solitus) in Panels A and B. In Panels C and D it enters the anatomically right atrium placed on the left, the characteristic feature of situs inversus. LA = anatomically left atrium, LV = anatomically left ventricle.

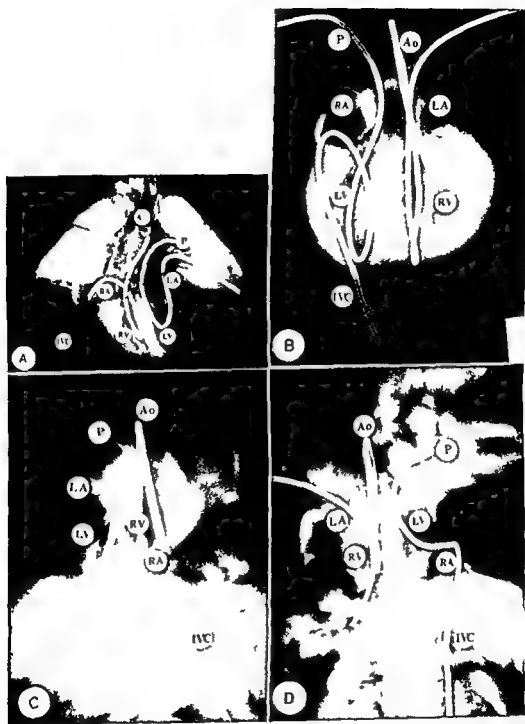


Fig 4 A through D Postmortem radiological studies with catheters placed in the cardiac chambers and the great arteries (frontal views). Identification of the ventricular chambers by means of the spatial relation of the two great arteries between themselves. Panels A-D illustrate hearts with transposition of the great arteries. A Transposition of the great arteries in situ solutus without ventricular inversion. B Transposition of the great arteries in situ solutus (mirror image dextrocardia). C Transposition of the great arteries in situs inversus without ventricular inversion (mirror image dextrocardia). D Transposition of the great arteries in situs inversus with ventricular inversion (mirror image dextrocardia). Notice that in every case both arteries are parallel and this indicates that there is transposition of the great vessels. In Panels A and D the catheter placed in the aorta (Ao) is parallel and placed on the right side of the catheter in the pulmonary artery (P) which indicates that the anatomically right ventricle (RV) is placed on the right. In Panels B and C the catheter placed in the aorta is parallel and placed on the left of the catheter within the pulmonary artery, indicating that the anatomically right ventricle is placed on the left side. RA = anatomically right atrium. LV = anatomically left atrium. LA = anatomically left ventricle. IVC = inferior vena cava.

the presence of one or two vessels arising from the heart (2) the spatial relations of the great arteries between themselves should be determined (3) the size of each of the arteries should be given with respect to the size of normal arteries and (4) the relations of these arteries with the ventricles should be established

1 Define whether there are one or two arteries arising from the heart When one artery emerges from the heart the diagnosis of persistent truncus arteriosus is made and this should be differentiated from pulmonary atresia with biventricular aorta in its two varieties—with transposition of the great arteries or without transposition of the great arteries¹ (extreme tetralogy of Fallot) In the case of a truncus arteriosus both branches of the pulmonary artery arise directly from this trunk or by way of a vessel which embryologically is the cephalic portion of the pulmonary artery There should not be a fibrous cord representative of this artery In the angiographic study of pulmonary atresia with biventricular aorta the branches of the pulmonary artery are filled through a patent ductus arteriosus since the trunk of this artery is represented by a fibrous cord

2 Establishment of the spatial relations of both vessels with each other in order to determine the three truncocoal morphologies^{1b} which may be present (a) straight and parallel great arteries in the sagittal plane therefore anterior aorta and posteriorly placed pulmonary artery (transposition of the great arteries) (b) parallel arteries in the frontal plane (partial distortion) and (c) crossed arteries in space therefore anteriorly placed pulmonary artery at its origin with respect to the aorta This latter group includes the normal pedicle and that of every congenital cardiopathy with two great arteries (with the exception of transposition of the great arteries in all of its varieties) and the partial distortions among which is the Taussig Bing complex

3 Determine the size of the great arteries with respect to the normal size The pulmonary artery may exhibit a larger than normal caliber which is seen in atrial septal defect or it may be narrow as seen in the tetralogy of Fallot The aorta may exhibit the same variations in size seen in the pul-

monary artery For example there is a variety of Eisenmenger's complex with a narrow aorta smaller than normal

4 Establishment of the relations of the great arteries with the ventricles The anterior infundibulum always corresponds to the anatomically right ventricle, while the posterior infundibulum belongs to the anatomically left ventricle When there is transposition of the great arteries the aorta is the anterior artery and therefore it arises from the anterior infundibulum which belongs to the anatomically right ventricle while the pulmonary artery arises from the posterior infundibulum which belongs to the anatomically left ventricle (Figs 6 B and 7 B₁) However if there is a concomitant lateral position (dextroposition) the pulmonary artery will continue to be the posterior vessel and it will override the interventricular septum or else it will arise from the anatomically right ventricle behind the aorta² (Figs 6 A₂ and 7 A₂) If the great arteries cross each other in space the anterior vessel which is the pulmonary artery will arise from the anterior infundibulum belonging to the anatomically right ventricle and the aorta will arise from the posterior infundibulum belonging to the left ventricle (Fig 6 B₁ and Fig 7 B₁) But if there is in addition a dextroposition the aorta will continue to be a posterior vessel and it may override the interventricular septum or else it may arise from the anatomically right ventricle behind the pulmonary artery² (Fig 6 A₁ and Fig 7 A₁)

Anatomical and spatial identification of the ventricles*

The spatial identification of the ventricles is important to diagnose the normal or inverted position in each of the situs that is the atrioventricular concordance or discordance in a given situs For instance the normal position of the ventricles for situs solitus is the situation in which the anatomically right ventricle is placed on the

The anatomically right ventricle is the one which has the pulmonary artery arising from it and the aorta arising from the left ventricle In the normal position the right ventricle is anterior and to the right of the left ventricle In the inverted position the right ventricle is posterior and to the left of the left ventricle In the transposed position the right ventricle is anterior and to the left of the left ventricle In the dextrotransposed position the right ventricle is posterior and to the right of the left ventricle

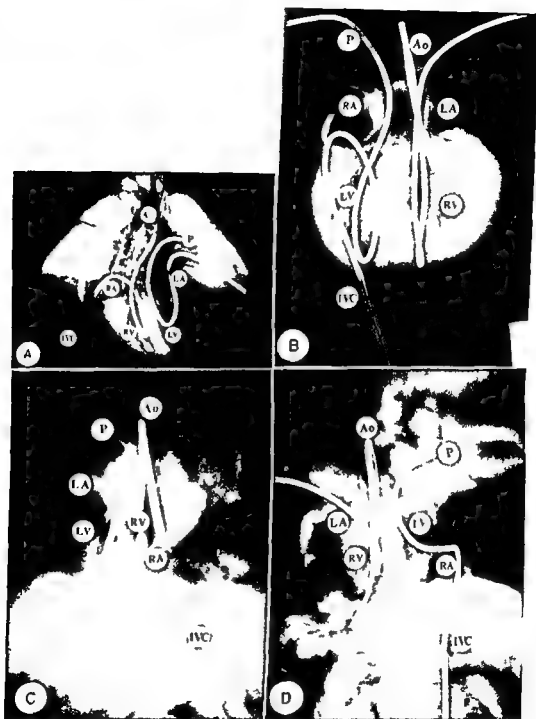


Fig. 4 *A* through *D* Postmortem radiological studies with catheters placed in the cardiac chambers and the great arteries. Frontal views. Identification of the ventricular chambers by means of the spatial relation of the two great arteries between themselves. Panels 1-*D* illustrate hearts with transposition of the great arteries. *A* Transposition of the great arteries in situs solitus without ventricular inversion. *B* Transposition of the great arteries in situs solitus with ventricular inversion (mirror image dextrocardia). *C* Transposition of the great arteries in situs inversus without ventricular inversion (mirror image dextrocardia). *D* Transposition of the great arteries in situs inversus with ventricular inversion (mirror image dextrocardia). Notice that in every case both arteries are parallel and this indicates that there is transposition of the great vessels. In panels *A* and *D* the catheter placed in the aorta (*Ao*) is parallel and placed on the right side of the catheter in the pulmonary artery (*P*) which indicates that the anatomically right ventricle (*RV*) is placed on the right. In panels *B* and *C* the catheter placed in the aorta is parallel and placed on the left of the catheter within the pulmonary artery indicating that the anatomically right ventricle is placed on the left side. *RA* = anatomically right atrium. *LA* = anatomically left atrium. *LV* = anatomically left ventricle. *IVC* = inferior vena cava.

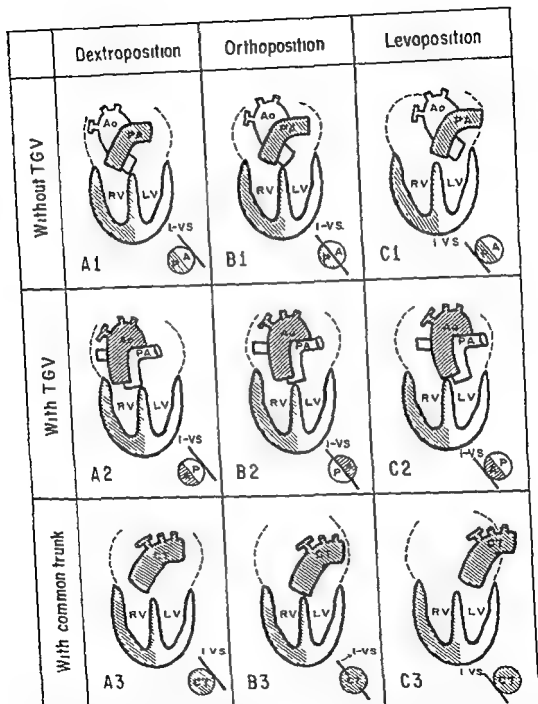


Fig 6 Lateral positions in situs solitus without ventricular inversion or in situs inversus with ventricular inversion. Diagrams representing the different truncoconal morphologies as a sign for the identification of the spatial position of the ventricular chambers. In the case of crossed arteries the direction from right to left of the pulmonary artery (PA) indicates that the anatomically right ventricle (RV) is placed on the right in the case of transposed arteries the right sided position of the aorta (Ao) with respect to the pulmonary artery indicates the right sided position of the anatomically right ventricle. The direction from right to left of the common trunk (CT) indicates that the anatomically right ventricle is placed on the right side. LV = anatomically left ventricle. TC = transposition of the great vessels.

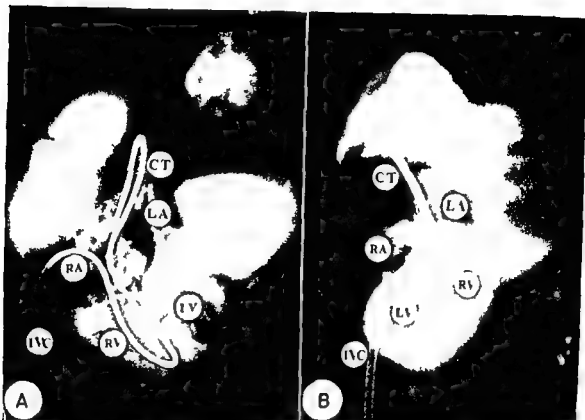


Fig 5 *A* and *B* Radiologic postmortem studies with catheters placed in the cardiac cavities and the great arteries. Frontal views. The two pictures correspond to hearts with a common trunk. Identification of the ventricular chambers by means of the direction of the common trunk. *A* Common trunk in situs solitus with out ventricular inversion. *B* Common trunk in situs solitus with ventricular inversion. Notice that in both cases a single vessel arises from the heart. In Panel *A* the common trunk (CT) is directed from right to left indicating that the anatomically right ventricle (RV) is placed on the right. In Panel *B* the direction of the common trunk from left to right testifies to the fact that the anatomically right ventricle is placed on the left side. RA = anatomically right atrium. LA = anatomically left atrium. LV = anatomically left ventricle. IVC = inferior vena cava.

right connecting with the anatomically right atrium placed on the same side¹⁹ (Figs 1*B*, 3*A*, 4*A* and 5*A*) and the ab normal position (ventricular inversion or atrioventricular discordance) for this situs is the anatomically left ventricle placed on the right side and connecting with the anatomically right atrium placed on the right (normal atrial position for situs solitus)¹⁹ (Figs 1*C*, 3*B*, 4*B* and 5*B*).

The normal position of the ventricles in a situs inversus is a situation in which the anatomically left ventricle is placed on the right and is therefore connected with the anatomically left atrium placed on the right¹⁹ (Figs 2*B*, 3*C*, and 4*C*). The ab normal position of the ventricles (ventricular inversion or atrioventricular discordance for this situs) is that in which the anatomically right ventricle is placed on the right and connects with the anatomically

left atrium placed on the right (normal atrial position for situs inversus)¹⁹ (Figs 2*C*, 3*D*, and 4*D*). The nomenclature of 'ventricular situs solitus' or situs inversus² is unacceptable because the normal or inverted position of these chambers depends on the situs of which they are a part. Thus the anatomically right ventricle on the right side is the normal position in situs solitus but it is an abnormal situation — i.e. ventricular inversion if it is within the context of a situs inversus (compare Figs 1*B* and 3*A* with Figs 2*C* and 3*D*).

In order to determine the position of the ventricles we have first to place them in space and then integrate them within the situs of which they are a part and which has been previously diagnosed. The spatial position of the ventricles is determined by utilizing the elements given by the analysis of the truncoconal morphology. The integration of

the ventricles within a given situs is established by correlating the position of the ventricles with the anatomically right atrium the suprahepatic portion of the inferior vena cava and the major lobe of the liver which are the elements that identify the situs

The designation of d loop² to establish the position of the ventricles is erroneous from the semantic point of view because it designates the position of a specific anatomic structure of the fetal and postnatal heart such as the ventricles using a nomenclature which is meant for the identification of a type of characteristic cardiac morphology which is only present in an embryonic stage of the development of this organ¹⁴ On the other hand this nomenclature has no significance if it is not referred to a given situs For instance the d loop in r situs inversus is a ventricular inversion since the anatomically left atrium placed on the right connects with the anatomically right ventricle placed on the right (Figs 2C 3D and 4D) In situs solitus on the contrary it means that there are normal atrioventricular relations since the anatomically right atrium placed on the right connects with the anatomically right ventricle also placed on the right (Figs 1B 3A 4A and 5A) In the same manner the l loop in situs inversus established the normal atrioventricular relations for this situs since the anatomically left atrium placed on the right connects with the anatomically left ventricle placed on the right (Figs 2B 3C and 4C) and in situs solitus it is a ventricular inversion since the anatomically right atrium placed on the right connects with the anatomically left ventricle placed on the right (Figs 1C 3B and 4B)

The rules for the diagnosis of the spatial position of the ventricles are conditioned by the type of truncocoanal morphology of the hearts—great arteries which cross in place (without transposition of the great arteries) transposition of the great arteries or truncus arteriosus communis

1 *Great arteries crossed in space* When the two great arteries are crossed in space the pulmonary artery is always the anterior vessel and therefore it arises from the anatomically right ventricle²⁷ In order to make sure of the position of this ventricle

in space it is necessary to determine the direction of the pulmonary artery The hemodynamic and angiocardigraphic diagnosis is made by means of a lateral x ray plate in order to demonstrate that the pulmonary artery is anterior with respect to the aorta and is posteroanterior (frontal) x ray film in order to determine the direction of the pulmonary artery If this artery goes from right to left the anatomically right ventricle is placed on the right (Figs 1D 2G 3A and 3D) if it is directed from left to right the anatomically right ventricle is placed on the left (Figs 1G 2D 3B and 3C) Furthermore in both directions of the pulmonary artery the valvular plane is higher than the plane of the aorta

2 *Transposition of the great arteries* In transposition of the great arteries the aorta is the anterior vessel and therefore it arises from the anterior infundibulum which belongs to the anatomically right ventricle² this element by itself does not permit us to ascertain the spatial position of this ventricle so that it becomes necessary to establish the relation of the pulmonary artery with respect to the aorta The hemodynamic and angiocardigraphic diagnosis is done by means of a lateral x ray film in order to demonstrate that the aorta is anterior with respect to the pulmonary artery and a frontal x ray film in order to determine the position of the aorta with respect to the pulmonary artery If the aorta is on the right side of the pulmonary artery the anatomically right ventricle is on the right side (Figs 1E 2H 4A and 4D) and if the aorta is on the left side of the pulmonary artery the anatomically right ventricle is on the left side (Figs 1H 2E 4B and 4C) In transposition of the great arteries the level of the valve cusps of the aorta is always higher than that of the pulmonary artery

The designation of d transposition² (anterior aorta to the right of the pulmonary artery which indicates that the anatomically right ventricle is placed on the right) and that of l transposition² (anterior aorta placed on the left side of the pulmonary artery which indicates that the anatomically right ventricle is placed on the left side) has no meaning unless one relates it

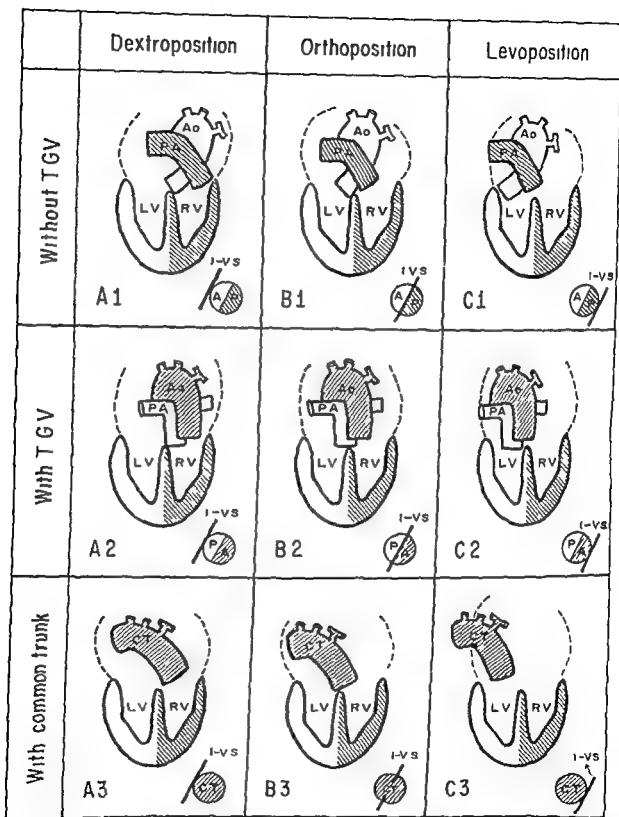


Fig. 7. Lateral positions in situs inversus without ventricular inversion or in situs solitus with ventricular inversion. Diagrams representing the different transposition morphologies as a sign for the identification of the spatial position of the ventricular chambers. In the case of crossed arteries, the direction from left to right of the pulmonary artery (PA) indicates that the anatomically right ventricle (RV) is placed on the left. In the case of transposed arteries the left sided position of the aorta (Ao) with respect to the pulmonary artery indicates the left sided position of the anatomically right ventricle. The left to-right direction of the common trunk (CT) indicates that the anatomically right ventricle is placed on the left side. LV = anatomically left ventricle. TGV = transposition of the great vessels.

group of truncoconal morphologies are not the object of this study because of their peculiar anatomic and embryologic features which do not conform to the rules given for the localization of the ventricles

Diagnosis of the size of the cardiac chambers

The inspection of the atria is important in order to ascertain their size—either normal, small or enlarged. For instance, right atrial enlargement along with other signs is a very valuable sign in the diagnosis of atrial septal defects, while a small left atrium associated with other cardiac anatomic signs is an indirect sign of a total anomalous pulmonary venous connection.

In the examination of the ventricles it is important to determine if they are normal, enlarged or small. In order to define their dimensions one must previously establish the external limits of each one of them by means of the path of the coronary arteries—the anterior descending and the posterior descending—which indicate indirectly the position of the ventricular septum, of the atrioventricular grooves which point the atrioventricular valvular level and also to determine the borders of the heart at the ventricular level. There is an indirect sign which permits one to suspect if the anatomically right ventricle is enlarged due to hypertrophy or to dilatation. This information is supplied by the aspect of the external border of this ventricle: if it is sharp it indicates hypertrophy, and if it is blunt it depicts dilatation. This sign is not useful or applicable to the study of hypertrophy or dilatation of the anatomically left ventricle because of the ventricle's normal concave shape.

A small anatomically left ventricle is a sign of most importance in the diagnosis of congenital mitral stenosis along with the study of other cardiac signs.

The presence of the anterior and posterior descending coronary arteries represented by two small branches similar to other numerous vertical branches which arise from the coronary arteries in their course, along the atrioventricular grooves, strongly suggests the diagnosis of a single ventricle, but the absence of this sign does not exclude such a diagnosis.

Summary

A series of rules for the diagnosis of visceral situs truncoconal morphologies, spatial position of the ventricles and atrioventricular relations are presented. These rules are based on anatomoembryologic concepts and therefore they are applicable to the radiologic and angiocardigraphic study of congenital cardiopathies.

1. A situs solitus is characterized because of the presence of an anatomically right atrium placed on the right which is identified radiologically by the right sided position of the suprahepatic portion of the inferior vena cava. Situs inversus is characterized by an anatomically right atrium placed on the left which is identified radiologically by the left position of the suprahepatic portion of the inferior vena cava.

2. In order to diagnose truncoconal morphologies it is necessary to specify first the presence of one or two arteries arising from the heart. If a single artery arises from the heart it is a common trunk. When two arteries arise from the heart there are two main truncoconal morphologies: (a) the arteries cross each other in space—the pulmonary artery crosses obliquely in front of the aorta and (b) transposition of the great arteries—the aorta is then anterior and parallel to the pulmonary artery.

3. By means of the truncoconal morphologies the spatial position of the ventricles is identified. When the arteries cross each other (without transposition) the right to left direction of the pulmonary artery indicates that the anatomically right ventricle is placed on the right side and vice versa. When the great arteries are transposed the right-sided position of the aorta with respect to the pulmonary artery indicates that the anatomically right ventricle is on the right side and vice versa. The direction of the common trunk from right to left indicates the right sided position of the anatomically right ventricle and vice versa. This rule is also valid for later positions of the great arteries (dextro- and levopositions).

4. Once the visceral situs is diagnosed by means of the position of the suprahepatic segment of the inferior vena cava and the spatial position of the ventricles

with the type of situs of which they form part. Thus a d transposition in a situs solitus causes the anatomically right atrium to connect with the aorta through an anatomically right ventricle placed on the right and gives rise to the clinical picture of transposition of the great arteries (Figs 1E and 4A). The d transposition in situs inversus on the other hand, causes the anatomically left atrium to communicate with the aorta through an anatomically right ventricle placed on the right without any hemodynamic consequence if there are no added malformations, since it is a ventricular inversion with transposition of the great arteries also designated as "corrected transposition of the great arteries" although this latter designation seems to us incorrect (Figs 2H and 4D).

3 Common trunk In common trunk the important feature is the direction of the single vessel in space. If it is directed from the right to the left the anatomically right ventricle is placed on the right side (Figs 1F, 2I and 5A). If it is directed from left to right the anatomically right ventricle is placed on the left side (Figs 1I, 2F and 5B). The hemodynamic and angiocardio graphic diagnosis is made with a frontal x ray film.

Regardless of the absence of a truncocoel septum (common trunk) or of a straight septum (transpositions) or of a rotated septum (great arteries which cross each other in space), the truncus conus in the embryo connects with the anatomically right ventricle and later becomes displaced toward the midline in order to become biventricular which is the normal position (orthoposition).¹⁷ If the truncus conus remains in the embryonic position a dextroposition takes place in which both vessels or the common trunk arise from the anatomically right ventricle or a vessel arises from this ventricle and the other one overrides the ventricular septum (dextropositions) (Fig 6A₁, A₂ and A₃ and Fig 7A₁, A₂ and 1a). If there is an ab normal displacement and the truncus conus remains connected with the anatomically left ventricle both vessels or the common trunk arise from this ventricle or one of them overrides the septum and the other one arises from the anatomically left ven-

tricle (levopositions)¹⁸ (Fig 6C₁, C₂ and C₃ and Fig 7C₁, C₂ and C₃).

The rules for orthoposition are valid for the location of the ventricles through the truncocoel morphologies both in levopositions and in dextropositions. For instance in the case of arteries which cross each other in space the right to left direction of the pulmonary artery indicates that the anatomically right ventricle is placed on the right side, even though (1) the great arteries arise from this ventricle or (2) both of them arise from the anatomically left ventricle or (3) else one of them overrides the septum and the other one arises from the anatomically right or left ventricle (Fig 6A₁, B₁, and C₁).

In general, in levopositions the anatomically right ventricle is hypoplastic in spite of which the rules previously mentioned apply, since in these cases the ventricle that is properly developed has the anatomical features of the left ventricle.

In transposition of the great arteries the aorta placed on the left of the pulmonary artery indicates that the anatomically right ventricle is placed on the left side regardless of whether both arteries arise from this ventricle both from the anatomically left ventricle, or one of them overrides the septum and the other arises from the anatomically right or left ventricle (Fig 7A₂, B₂ and C₂).

After having located the ventricles spatially by means of the study of the truncocoel morphologies the relation of the ventricles with their atria is established—that is with the viscerotransital situs of which they are part (anatomically right atrium suprahepatic portion of the inferior vena cava greater lobe of the liver). For instance, if the anatomically right ventricle is placed on the left and connects with the atrium which receives the suprahepatic portion of the inferior vena cava and the greater lobe of the liver is placed on the left the diagnosis of normally placed ventricles in situs inversus is made (Fig 2B and 3C) however if it connects with an atrium which does not have that vein and the greater lobe of the liver is on the right it is a ventricular inversion in situs solitus (Figs 1C and 3B).

Partial distortions although merely a

Pulmonary cineangiography in acute pulmonary embolism

Steven G. Meister MD

Harold L. Brooks MD

Murrill W. Sacks MD

John S. Banas Jr MD

Lewis Dexter MD

James F. Dalen MD

Boston, Mass

Pulmonary angiography is widely accepted as the most definitive technique available for the diagnosis of acute pulmonary embolism.¹ The angiographic abnormalities that are diagnostic of acute pulmonary embolism are intraluminal filling defects and/or arterial cutoffs.^{2,3} However, in our experience the primary limitation of this technique is that some angiographic studies are equivocal because it is not possible to be certain of the presence of these two diagnostic abnormalities. In a series of 247 consecutive patients with suspected pulmonary embolism studied by conventional cut film pulmonary angiography we noted equivocal results in 17 per cent.⁴

This study was undertaken to determine if selective pulmonary cineangiography—used as an adjunct to conventional pulmonary angiography—could be useful in establishing a definitive diagnosis in equivocal cases.

Materials and methods

Patient selection. Pulmonary cineangiography was performed in 14 patients whose

conventional cut film angiographic studies were equivocal for acute pulmonary embolism. Cineangiography was also performed in 22 additional patients whose conventional angiographic study had been definitive—i.e. positive for pulmonary embolism in 16 and negative in 6. The total incidence of equivocal results by conventional pulmonary angiography during the time of this study was 16 per cent.

Angiographic techniques. Conventional pulmonary angiography was performed by previously described techniques.⁵ Sixty ml of contrast medium was injected into the main pulmonary artery or right ventricular outflow tract at an injection rate of 25 to 30 ml per second. Twelve films were taken at a rate appropriate to visualize arterial, capillary, and venous phases. When indicated repeat cut film angiograms with selective injection into areas in question were performed with oblique projections.

Pulmonary cineangiograms were performed by injecting 20 to 30 ml of contrast medium into the main right or left pulmonary arteries or their first order subdivisions at 15 to 20 ml per second utilizing a closed

From the Department of Medicine, Peter B. P. Brigham Hospital, a Joint Harvard Medical School, Boston, Massachusetts. This study was supported in part by U.S. State Department Health Service Grant HE-12439 and HE-05679.

Received for publication August 27, 1971.

Reprint requests to James F. Dalen, MD, Peter B. P. Brigham Hospital, 721 Huntington Avenue, Boston, Massachusetts 02115.

is ascertained by means of the truncocoaral morphologies one proceeds to establish the atrioventricular relations which number two for each situs—normal atrioventricular relation (atrioventricular concordance) or ventricular inversion (atrioventricular discordance)

REFERENCES

- 1 Lev M and Rowlett U F The pathologic anatomy of mixed levocardia: A review of thirteen cases of atrial or ventricular inversion with or without corrected transposition. *Am J Cardiol* 8:216 1961
- 2 Van Praagh R, Van Praagh S, Vlod P and Keith J D Anatomic types of congenital dextrocardia: Diagnostic and embryologic implications. *Am J Cardiol* 13:510 1964
- 3 Calderón J, Márquez J, Cerezo I, Sánchez F, Azar V and Torrecilla I Dextrocardia con aurícula in situ solita. *Cardiologia* 18:40 1965
- 4 Campbell M and Deuchar D C Dextrocardia and isolated levocardia. II Situs inversus and isolated dextrocardia. *Br Heart J* 28:472 1966
- 5 Stanger P, Benassi K, Cohns M F, Jue K L and Edwards J F Diagrammatic portrayal of variations in cardiac structure. Reference to transposition dextrocardia and the concept of four normal hearts. *Circulation* 37 (Supplement IV):6 1968
- 6 Padmanabhi S and Gupta S Partial situs in versus with levocardia: An unusual combination of anomalies. *Circulation* 26:108 1962
- 7 Hinson J S and Tabakin B S Primary and secondary dextrocardia: Their differentiation and the role of cineangiocardigraphy in diagnosing associated congenital cardiac defects. *Am J Cardiol* 8:275 1961
- 8 Berri G G Dextrocardia y levocardia. Buenos Aires 1958. *Ilustraciones Gráficas Didot S R L*
- 9 Hinson J S and Tabakin B S Primary and secondary dextrocardia: Their differentiation and the role of cineangiocardigraphy in diagnosing associated congenital cardiac defects. *Am J Cardiol* 8:275 1961
- 10 Campbell M and Deuchar D C Dextrocardia and isolated levocardia. I Isolated levocardia. *Br Heart J* 27:69 1965
- 11 Anclau G, Munoz S, Machado J, Blanco P and Espino-Vela J Complex cardiovascular malformations associated with the corrected type of transposition of the great vessels. *Am Heart J* 66:614 1963
- 12 Van Praagh R and Van Praagh S Anatomically corrected transposition of the great arteries. *Br Heart J* 29:112 1967
- 13 Lev M Autopsy diagnosis of congenitally malformed hearts. Springfield Ill 1953 Charles C Thomas Publisher
- 14 De la Cruz M V, Anclau G, Cisneros F, Reinhold M, Portillo B and Espino-Vela J An embryological explanation for the corrected transposition of the great vessels. Additional description of the main anatomic features of this malformation and its varieties. *Am Heart J* 57:1104 1959
- 15 Van Praagh R What is congenitally corrected transposition? *N Engl J Med* 282:1097 1970
- 16 Davis C I Development of the human heart from its first appearance to the stage four and embryos of twenty paired omes. *Contrib Embryol* 19:245 1927
- 17 Kramer T C The partitioning of the truncus and conus and the formation of the membranous portion of the interventricular septum in the human heart. *Am J Anat* 71:143 1947
- 18 Streeter G I Developmental horizon in human embryos. Description of age groups VI, VII, VIII and IX. Being the third volume of a survey of the Carnegie Collection. *Contrib Embryol* 32:133 1948
- 19 De la Cruz M V, Espino-Vela J, Attie F, and Munoz I An embryologic theory for ventricular inversions and their classification. *Am Heart J* 73:717 1967
- 20 De la Cruz M V, Anclau G, Munoz Castelinos I, Nadal Ginard B and Munoz Armas S Systematization and embryological and anatomical study of mirror image dextrocardia: dextroversions and levoversions. *Br Heart J* 33:841 1971
- 21 Munoz Armas S, Anclau A, de la Cruz M V and Vichado I Pulmonary atresia with biventricular aorta. *Br Heart J* 26:606 1964
- 22 De la Cruz M V and de Rocha J P An ontogenic theory for the explanation of congenital malformation involving the truncus and conus. *Am Heart J* 51:782 1956
- 23 Hallermann F J, Kuncord O W, Litter D G, Oueley I A and Titus J I Angiocardiographic and anatomic findings in one of both great arteries from the right ventricle. *Am J Congenital Heart Dis* 1:101 1970

Pulmonary cineangiography in acute pulmonary embolism

Steven G. Meister MD

Harold L. Brooks MD

Murrill V. Sacks MD

John S. Banas Jr MD

Lewis Dexter MD

James E. Dalen MD

Boston, Mass

Pulmonary angiography is widely accepted as the most definitive technique available for the diagnosis of acute pulmonary embolism.¹ The angiographic abnormalities that are diagnostic of acute pulmonary embolism are intraluminal filling defects and/or arterial cutoffs.^{2,3} However, in our experience the primary limitation of this technique is that some angiographic studies are equivocal because it is not possible to be certain of the presence of these two diagnostic abnormalities. In a series of 247 consecutive patients with suspected pulmonary embolism studied by conventional cut film pulmonary angiography we noted equivocal results in 17 per cent.⁴

This study was undertaken to determine if selective pulmonary cineangiography—used as an adjunct to conventional pulmonary angiography—could be useful in establishing a definitive diagnosis in equivocal cases.

Materials and methods

Patient selection. Pulmonary cineangiography was performed in 14 patients whose

conventional cut film angiographic studies were equivocal for acute pulmonary embolism. Cineangiography was also performed in 22 additional patients whose conventional angiographic study had been definitive—i.e. positive for pulmonary embolism in 16 and negative in 6. The total incidence of equivocal results by conventional pulmonary angiography during the time of this study was 16 per cent.

Angiographic techniques. Conventional pulmonary angiography was performed by previously described techniques.⁵ Sixty ml of contrast medium was injected into the main pulmonary artery or right ventricular outflow tract at an injection rate of 25 to 30 ml per second. Twelve films were taken at a rate appropriate to visualize arterial, capillary, and venous phases. When indicated repeat cut film angiograms with selective injection into areas in question were performed with oblique projections.

Pulmonary cineangiograms were performed by injecting 20 to 30 ml of contrast medium into the main right or left pulmonary arteries or their first order subdivisions at 15 to 20 ml per second utilizing a closed

From the Department of Medicine, Peter Bent Brigham Hospital and the Harvard Medical School, Boston, Mass. This study was supported in part by United States Public Health Service Grant HE-12439 and HE-05679. Received for publication August 27, 1971. Reprints request to James E. Dalen, MD, Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston, Mass 02115.

J. of the Am. Coll. of Physicians July 1972

lip angiographic catheter (Lidman) was at 64 frames per second using an Arriflex camera and a six inch image intensifier. Shutters were positioned to exclude high density anatomic structures such as adjacent heart border, spine, or diaphragm. Choice of positioning was dependent on the anatomy of the particular area to be visualized as determined by analysis of the conventional angiograms.

Interpretation of angiographic and cineangiographic results

Conventional angiograms were read by four to six of the investigators at the time of the study. Cineangiograms were interpreted by the same investigators when they were developed two to four hours later, with knowledge of the results of the conventional angiograms. Independent and/or individual evaluation of the two techniques was judged to be incompatible with optimum patient care and unnecessary in view of the intended use of cineangiography as a supplement to conventional angiography.

The diagnosis based upon each technique was then determined as being definitely positive, definitely negative or equivocal. Studies upon which agreement could not be reached by all investigators were listed as equivocal even though individual investigators considered them definitely positive or negative.

Results

Of the 16 patients in whom the results of conventional angiography were considered definitely positive, the use of cineangiography led to a change of diagnosis in only one (Table I). In this case (Table II, Case 1) the conventional angiogram was thought to show an intraluminal filling defect in the main artery to the left lower lobe. Cineangiography revealed entirely normal filling of the artery in question. However, as contrast medium was washed out of the large artery, more distally located smaller vessels still contained contrast medium and overlapped the larger vessel in such a manner as to simulate the appearance of a filling defect. In the other 15 patients whose conventional angiograms were positive, the cineangiogram showed abnormalities in the same arteries that had been abnormal by conventional angiography.

Of the six conventional angiographic studies considered definitely negative, no diagnosis was changed by the results of the cineangiographic studies (Table I). However, of the 14 conventional angiographic studies that had been equivocal, use of supplementary pulmonary cineangiography led to a definitive diagnosis in 13. In eight of these cases, the cineangiographic studies demonstrated no evidence of pulmonary embolism in the areas in question. In each instance a satisfactory explanation for the equivocal angiographic appearance was apparent. These mechanisms are detailed for the individual cases in Table II. In five other equivocal cases, cineangiographic studies delineated definite intraluminal filling defects or arterial cutoffs in the questionable areas. Thus the final diagnoses were changed to definite pulmonary embolism in these five cases. The cineangiographic findings which permitted a definitive diagnosis are listed for the individual cases in Table II. In one case the results were considered equivocal by both techniques.

Confirmation of angiographic and cineangiographic results

Postmortem confirmation of the combined angiographic and cineangiographic studies was obtained in two patients. One patient died six weeks after a study in which an equivocal angiographic diagnosis was changed to definitely positive by the cineangiographic study. In the interim she had received thrombolytic therapy followed by continuous anticoagulation. At autopsy the large vessels were clear, but large numbers of organizing thromboemboli were found in the smaller pulmonary arteries. The cause of death was unrelated to pulmonary embolism. A second patient died two weeks after a study that was positive by both techniques. Autopsy revealed massive pulmonary embolism, both old and new, arising from a mural thrombus on the right side of the infarcted ventricular septum.

Discussion

The angiographic abnormalities that are diagnostic of pulmonary embolism, namely filling defects and arterial cutoffs, are under some circumstances difficult to recognize.

Table I Influence of cineangiographic study on angiographic diagnosis

Angiographic diagnosis	Number	Final diagnosis—(angiogram and cineangiography)		
		Definite	Equivocal	Negative
Definite	16	15	0	1
Equivocal	14	5	1	8
Negative	8	0	0	6
	36			

Table II Cases in which final diagnosis was changed on basis of pulmonary cineangiography

Case	Conventional angiography ^a		Cineangiography	
	Findings	Diagnosis	Findings	Diagnosis
1	Definite Filling Defect RLI	Definite	Overlapping structures—no FD	Negative
2	Filling Defect RLL (?)	Equivocal	Overlapping structure no FD and no CO	Negative
3	Cutoff LLL (?)			
4	Cutoff RLL (?)	Equivocal	Stationary FD seen being enveloped by contrast medium	Definite
5	Filling Defect, RUL (?)	Equivocal	Small clot seen in motion	Definite
9	Linear Filling Defect LUL (?)	Equivocal	Parallel artery and vein opacity sequentially—no FD	Negative
15	Filling Defect and Cutoff LLL (?)	Equivocal	Long coiled clot seen in motion—one end impacted in LUL branch	Definite
16	Filling Defects RLL LLL (?)	Equivocal	Overlapping structures—no FD	Negative
17	Cutoff RLL (?)	Equivocal	Definite CO among several overlapping vessels in atelectatic segment	Definite
25	FD LLL (?)	Equivocal	Overlapping structures no FD	Negative
26	FDs RLL LLL (?)	Equivocal	Overlapping structures—no FD	Negative
28	FD RLI (?)	Equivocal	Stationary FD seen being enveloped by contrast medium	Definite
29	FD RLL (?)	Equivocal	Overlapping structures no FD	Negative
32	FD and CO RLI (?)	Equivocal	Continuity of flow through vessels distorted by bullae	Negative
33	FD RLL (?)	Equivocal	Overlapping structures no FD	Negative

Abbreviations: FD = filling defect; CO = cutoff; RLL = right lower lobe; LLL = left lobe; LUL = left upper lobe; RUL = right upper lobe.

or distinguish from other normal or abnormal anatomic structures in the lung. The value of supplemental pulmonary cineangiography in this setting derives from its capacity to delineate motion and flow characteristics.

For example intraluminal clots when they are incompletely obstructing may be obscured by contrast medium passing around them¹³ and can occasionally be

overlooked or be difficult to recognize on conventional angiograms. Cineangiography may permit visualization of such incomplete obstructions by revealing the complete sequence of movement of the contrast medium as it flows around and envelops the clot. Also if portions of the clot are pedunculated they may readily be seen moving during the rapid systolic flow. This is a striking finding when present and pro-

vided the basis for changing the diagnosis to positive in two patients whose conventional angiograms were considered to have been equivocal. It was also observed in several patients whose conventional angiograms had been positive.

The ability to perceive the details of sequential flow may be helpful in other situations. In one instance an artery was parallel to an adjacent pulmonary vein. When both were opacified the resultant radiolucent space between them closely resembled a linear filling defect within a single vessel on the conventional angiogram. The cineangiogram readily clarified the anatomy by demonstrating that the artery filled much earlier than the vein and from the opposite direction.

In our experience the commonest cause of difficulty in interpreting conventional angiograms is the presence of overlapping structures, which by addition or subtraction of radiodensity at critical points may simulate filling defects or cutoffs. Repeat angiograms in oblique projections are often helpful by changing the alignment of the overlapping structures. At times however this approach succeeds only in substituting another confusing array of overlapping structures. We have found cineangiography to be especially useful in this situation because of its ability to demonstrate relative motion between overlapping structures. This often allows differentiation of vessels from one another, from overlying bronchi or from portions of the cardiac shadow.

Similarly the ability to appreciate sequential filling and relative motion may be extremely helpful in distinguishing a true arterial cutoff from an artery that simulates this appearance by bifurcating into two end-on branches. Here cineangiographic visualization of slight moment to moment changes in orientation of the end-on branches as well as sequential appearance of their more distal branches often permits an accurate assessment of the anatomy.

Other techniques for enhancing the diagnostic accuracy of pulmonary angiography have been devised. In particular magnification angiography⁶ and multisession angiography⁷ have been reported to be useful in this regard.

We have not had the opportunity to

compare pulmonary cineangiography with either of these techniques. Cineangiography does however have one advantage relative to either of them in that it is readily available in nearly all laboratories that perform cardiac catheterization and related procedures.

A disadvantage of pulmonary cineangiography is the relatively longer time required for film development. Our preliminary experience with using a video tape recorder for instant playback of the cine results has been quite favorable in spite of the inherent small loss of resolution.

No complications were encountered with the use of cineangiography. In general there was less flushing, nausea, and coughing with the cineangiographic studies than with conventional angiography. This was probably due to the fact that smaller amounts of contrast medium were injected for the cineangiographic studies.

Conclusions

Selective pulmonary cineangiography was found to be a safe and useful adjunct to conventional pulmonary angiography. Its ability to show relative motion between overlapping structures and the details of flow within the pulmonary arteries can be very useful in arriving at a definite diagnosis when the results of conventional angiography are equivocal.

Summary

The usefulness of selective pulmonary cineangiography as a supplement to conventional pulmonary angiography was evaluated in 36 patients. In 13 of the 14 patients whose conventional angiographic results were equivocal pulmonary cineangiography of questionable accuracy permitted a definitive diagnosis to be made. In 21 of the 22 patients whose conventional angiographic studies were considered definitely positive or negative the cineangiographic results were in complete agreement. Thus the principal value of supplemental pulmonary cineangiography is in patients whose conventional angiograms yield equivocal results. Its usefulness in this situation derives from its ability to delineate the details of flow and motion within the pulmonary vasculature.

REFERENCES

- 1 Dalen J E Pulmonary angiography in pulmonary embolism *Bull Lhygiopath Exp* 6:45 1970
- 2 Stein P D O'Connor J F Dalen J E Fur Shihrian A V Hoppin F G Jr Hammond D T Haynes F W Fleischner F G and Dexter L The angiographic diagnosis of acute pulmonary embolism. Evaluation of criteria *Am Heart J* 73:730 1967
- 3 Dalen J E Brooks H L Johnson L W Meister S G Szucs M M Jr and Dexter L Pulmonary angiography in acute pulmonary embolism. Indications techniques and results in 367 patients *Am Heart J* 81:175 1971
- 4 Lowman R M Reardon J Hipona F A Stern H and Toole A The role of pulmonary angiography in pulmonary embolism *Angiology* 18:791 1967
- 5 Dalen J E Mathur V S Evans H Haynes F W Fur Shihrian A A Stein P D and Dexter L Pulmonary angiography in experimental pulmonary embolism *Am Heart J* 72:509 1966
- 6 Greenpan R H Simon A L Ricketts H J Pojas P H and Watson J C In vivo magnification angiography *Invest Radiol* 2:419 1967

vided the basis for changing the diagnosis to positive in two patients whose conventional angiograms were considered to have been equivocal. It was also observed in several patients whose conventional angiograms had been positive.

The ability to perceive the details of sequential flow may be helpful in other situations. In one instance an artery was parallel to an adjacent pulmonary vein. When both were opacified the resultant radiolucent space between them closely resembled a linear filling defect within a single vessel on the conventional angiogram. The cineangiogram readily clarified the anatomy by demonstrating that the artery filled much earlier than the vein and from the opposite direction.

In our experience, the commonest cause of difficulty in interpreting conventional angiograms is the presence of overlapping structures which by addition or subtraction of radiodensity at critical points may simulate filling defects or cutoffs. Repeat angiograms in oblique projections are often helpful by changing the alignment of the overlapping structures. At times however this approach succeeds only in substituting another confusing array of overlapping structures. We have found cineangiography to be especially useful in this situation because of its ability to demonstrate relative motion between overlapping structures. This often allows differentiation of vessels from one another from overlying bronchi or from portions of the cardiac shadow.

Similarly, the ability to appreciate sequential filling and relative motion may be extremely helpful in distinguishing a true arterial cutoff from an artery that simulates this appearance by bifurcating into two end-on branches. Here cineangiographic visualization of slight moment to moment changes in orientation of the end-on branches as well as sequential appearance of their more distal branches often permits an accurate assessment of the anatomy.

Other techniques for enhancing the diagnostic accuracy of pulmonary angiography have been devised. In particular magnification angiography⁶ and multisection angiography⁴ have been reported to be useful in this regard.

We have not had the opportunity to

compare pulmonary cineangiography to either of these techniques. Cineangiography does however have one advantage relative to either of them in that it is readily available in nearly all laboratories that perform cardiac catheterization and related procedures.

A disadvantage of pulmonary cineangiography is the relatively longer time required for film development. Our preliminary experience with using a video tape recorder for instant playback of the cine results has been quite favorable in spite of the inherent small loss of resolution.

No complications were encountered with the use of cineangiography. In general there was less flushing, nausea, and coughing with the cineangiographic studies than with conventional angiography. This was probably due to the fact that smaller amounts of contrast medium were injected for the cineangiographic studies.

Conclusions

Selective pulmonary cineangiography was found to be a safe and useful adjunct to conventional pulmonary angiography. Its ability to show relative motion between overlapping structures and the details of flow within the pulmonary arteries can be very useful in arriving at a definitive diagnosis when the results of conventional angiography are equivocal.

Summary

The usefulness of selective pulmonary cineangiography as a supplement to conventional pulmonary angiography was evaluated in 36 patients. In 13 of the 14 patients whose conventional angiographic results were equivocal pulmonary cineangiography of questionable areas permitted a definitive diagnosis to be made. In 21 of the 22 patients whose conventional angiographic studies were considered definitely positive or negative the cineangiographic results were in complete agreement. Thus, the principal value of supplemental pulmonary cineangiography is in patients whose conventional angiograms yield equivocal results. Its usefulness in this situation derives from its ability to delineate the details of flow and motion within the pulmonary vasculature.

REFERENCES

- 1 Dalen J E. Pulmonary angiography in pulmonary embolism. *Bull. Physiother. Resp.* 6:45, 1970.
- 2 Stein P D, O'Connor J F, Dalen J E, Pur Shahrari A A, Hoppin F G Jr, Hammond D T, Haynes F W, Fleischner F G, and Dexter L. The angiographic diagnosis of acute pulmonary embolism. Evaluation of criteria. *Am Heart J* 3:730, 1967.
- 3 Dalen J E, Brooks H L, Johnson L W, Meister S G, Struss M M Jr, and Dexter L. Pulmonary angiography in acute pulmonary embolism. Indications, techniques, and results in 367 patients. *Am Heart J* 81:173, 1971.
- 4 Lowman R M, Leonard J, Hipona F A, Stern H, and Toole A. The role of pulmonary angiography in pulmonary embolism. *Angiology* 18:291, 1967.
- 5 Dalen J E, Mathur V S, Evans H, Haynes F W, Pur Shahrari A A, Stein P D, and Dexter L. Pulmonary angiography in experimental pulmonary embolism. *Am Heart J* 72:509, 1966.
- 6 Greenpan R H, Simon A L, Ricketts H J, Pujas R H, and Watson J C. In vivo migration angiography. *Invest. Radiol.* 2:119, 1967.

Incomplete bilateral bundle branch block and A-V block complicating acute anterior wall myocardial infarction

Sidney Fenn MD
Lazar Fichstein MD
New York NY

In recent years physicians have become aware of the high mortality rate of complete heart block (CHB) associated with acute anterior wall myocardial infarction (MI). Norris¹ noted a 5 per cent incidence of CHB with acute anterior wall MI and a 75 per cent mortality rate in this group. Lasser and Julien noted that 10 of their 11 patients with anterior wall MI who developed CHB died. Similar findings were also reported by Friedberg and associates.²

Since the mortality rate of this condition is high attention has been focused on recognizing electrocardiographic (ECG) patterns which will help in predicting the onset of CHB or asystole. Godman and associates⁴ stress the importance of a bilateral bundle branch block pattern preceding the appearance of CHB. These investigators reported that 75 per cent of a group of patients with acute MI developed CHB shortly after a pattern of bilateral bundle branch block was recognized. The mortality rate in this group was extremely high (18 of 21 died).

During a five year period (1965-1970) 30 patients with acute anterior wall myocardial infarction complicated by CHB or

a form of incomplete bilateral bundle branch block (IBBBB) were managed in a coronary care unit. The purpose of this report is to review our experience with this group with particular reference to ECG and clinical features of prognostic importance and to evaluate the role of artificial pacing in management.

Methods

Definitions: Confirmation of acute MI required abnormal Q waves and serial ST T changes as well as characteristic serum creatinine phosphokinase and transaminase abnormalities. The classification used for anterior wall infarction included the criteria of Meyers and associates⁸ for antero-septal and anterolateral MI.

Right bundle branch block (RBBB) and left bundle branch block (LBBB) were defined according to the criteria of the New York Heart Association and included a QRS duration of 0.12 second or more. Patients with RBBB and a Q wave in V₁ were not listed separately.

The following criteria were employed for the diagnosis of incomplete bilateral bundle branch block (IBBBB) variant as observed

[illegible]

among our patients RBBB with left anterior hemiblock (LAHB) RBBB with left posterior hemiblock (LPHB) alternating LBBB and RBBB in the same or in serial tracings first-degree A V with bundle branch block and unusually prolonged QRS⁸ and Mobitz type II A V block.

Mobitz type II A V block is defined as failure of a ventricular response without antecedent progressive lengthening of the A V conduction time.⁹ This type of A V block has been classified as one of the ECG manifestations of bilateral bundle branch block.⁸ It is recognized that exceptions exist¹⁰ but this would require His bundle recording for documentation.

Patients and procedures There were 18 men (average age 66 range 39 to 80) and 12 women (average age 74 range 59 to 86). A history of antecedent heart disease could be obtained in only ten patients. Any patient with previous ECG evidence of IBBB was excluded from the study.

The patients were followed in a coronary care unit with oscilloscopic monitoring at each bedside. All patients had a standard 12 lead ECG daily and more frequently if any evidence of A V or I V conduction defect was noted on the oscilloscope. Ventricular fibrillation or ventricular standstill were observed on the oscilloscope and in some cases were graphically recorded. Deaths due to terminal cardiogenic shock or congestive heart failure were not listed as arrhythmia deaths. During the first three years of this study temporary transvenous pacing electrodes were inserted only after the appearance of CHB or ventricular standstill. Over the last two years the indication for temporary pacing was expanded to include all patients with RBBB and IBBB patterns.

None of the patients was lost to follow up. The follow up period of surviving patients ranges from three years to seven months. Postmortem information is available on four patients.

Results

Of the total group of 30 patients 19 (63 per cent) died during their initial hospitalization. The initial hospitalization period was four weeks. There were two deaths in the fourth week but the majority occurred in the first week. There was one

late sudden death at eight months with cause undetermined.

Seven patients had no evidence of either A V or complete bundle branch block on admission (Table I). Two of these seven patients had LAHB on admission. Five patients developed CHB between the first and seventh day. In all cases CHB was preceded by some degree of intraventricular block by a period of several hours to two days. Of the two patients in this group who did not develop CHB one developed RBBB and LAHB on day 3. The RBBB disappeared on day 4 but the patient died in shock and congestive heart failure on day 10. The other patient who did not develop CHB had evidence of both inferior and anterior wall myocardial infarction and developed Mobitz type I A V block on day 3 and Mobitz type II A V block on day 4. He is alive at four months.

Fourteen patients presented with evidence of IBBB on admission (Table II). Within this group ten patients developed CHB or ventricular standstill within the first seven days. Six of the latter died. Two patients died in ventricular standstill before pacing could be initiated. One patient died suddenly (unmonitored) on day 23 one week after the pacemaker had been removed. The remaining three patients died in cardiogenic shock. Four patients continued with the pattern they had on admission. One with LAHB and RBBB is alive at four months; the other with first degree A V block LPHB and RBBB died in ventricular fibrillation on day 5. CHB occurred late in two patients: one on day 25 and another at 18 months.

Of four patients with RBBB on admission (Table III) one developed CHB (day 1) and two ventricular standstill (day 1 day 7). All three died—one in cardiogenic shock, one in CHB and one in ventricular standstill. The latter two patients died before pacing could be initiated. The fourth patient in this group developed IBBB (RBBB and LAHB) on day 3 and is alive at six months with this ECG pattern.

All three patients who had LBBB on admission (Table IV) died after developing CHB—two in shock and one in ventricular standstill.

Two patients had CHB on admission (Table V). One is alive at 14 months with a

Incomplete bilateral bundle branch block and A-V block complicating acute anterior wall myocardial infarction

Sidney Fung MD
Edgar Eichstein MD
New York, N Y

In recent years physicians have become aware of the high mortality rate of complete heart block (CHB) associated with acute anterior wall myocardial infarction (MI). Norris¹ noted a 5 per cent incidence of CHB with acute anterior wall MI and a 75 per cent mortality rate in this group. Lasser² and Julien³ noted that 10 of their 11 patients with anterior wall MI who developed CHB died. Similar findings were also reported by Friedberg and associates.⁴

Since the mortality rate of this condition is high attention has been focused on recognizing electrocardiographic (ECG) patterns which will help in predicting the onset of CHB or asystole. Godman and associates⁵ stress the importance of a bilateral bundle branch block pattern preceding the appearance of CHB. These investigators reported that 71 per cent of a group of patients with acute MI developed CHB shortly after a pattern of bilateral bundle branch block was recognized. The mortality rate in this group was extremely high (18 of 21 died).

During a five year period (1965-1970) 30 patients with acute anterior wall myocardial infarction complicated by CHB or

a form of incomplete bilateral bundle branch block (IBBBB) were managed in a coronary care unit. The purpose of this report is to review our experience with this group with particular reference to ECG and clinical features of prognostic importance and to evaluate the role of artificial pacing in management.

Methods

Definitions. Confirmation of acute MI required abnormal Q waves and serial ST-T changes as well as characteristic serum creatinine phosphokinase and transaminase abnormalities. The classification used for anterior wall infarction included the criteria of Meyers and associates^{6,7} for anteroapical and anterolateral MI.

Right bundle branch block (RBBB) and left bundle branch block (LBBB) were defined according to the criteria of the New York Heart Association and included a QRS duration of 0.12 second or more.⁸ Patients with RBBB and a Q wave in V₁ were not listed separately.

The following criteria were employed for the diagnosis of incomplete bilateral bundle branch block (IBBBBB) variant is observed

Printed by the City Hospital, Division of Medicine, Mount Sinai Hospital, City Hospital Center, New York, N.Y. 10021. Received for publication September 30, 1971.
Reprint requests to Edgar Eichstein, MD, Cardiology Division, Mount Sinai Hospital Services, City Hospital Center at 11th Street, 79-01 Broadway, Flushing, N.Y. 11375.

Table 11 Patients with LCG evidence of IBBB on admission

No	Age	Sex	ECG on admission	4:1 or 1:1 block	Pacemaker	Complications	Final disposition
8 T C	0	M	NSR Mobitz type I A V RBBB (QRS 0.12 sec)	CHB then ventricular standstill 5 hr			Died ventricular standstill 5 hr
9 S T	63	M	NSR LAHB RBBB	CHB (rate 60) day 7	Inserted day 4	Shock	Died day 4 shock
10 J M	64	F	NSR Mobitz type I A V LAHB RBBB	Ventricular standstill day 4	Inserted day 4	Shock day 8	Died, shock day 8
11 D P	5	M	NSR LAHB RBBB	Same	Inserted day 1 removed day 14	Mild CHF	Alive NSP LAHB PBBB 4 mo
12 E V	9	F	NSR LAHB PBBB	Mobitz type II 4:1 day 4 CHB (rate 45) day 5	Inserted day 1 removed day 0		Discharged day 4 CHB asymptomatic (patient) refused pacemaker
13 G H	5	M	NSR LAHB RBBB	Ventricular standstill day 1 LAHB day 2	Inserted day 1 removed day 14		Alive LAHB 1 yr
14 F G	40	F	NSR LAHB RBBB	Ventricular standstill day 9	Inserted day 1	Intermittent 9:1 block day 1	Died ventricular standstill day before pacing could be initiated
15 F P	73	F	NSR LAHB PBBB	NSR LBBB day 1 Mobitz type II 4:1 day 1 ventricular standstill day 1 atrial fibrillation LBBB day 3 NSR Mobitz type I A V with LBBB day 4	Inserted day 1 removed day 1	Mild CHF	Alive NSP Mobitz type I A V LBBB 13 mo
16 H M	30	F	NSP Mobitz type II A V PBBB	CHB day 1	Inserted day 1 permanent (demand) pacemaker 1 mo	Moderate CHF intermittent ventricular tachycardia	Died, 8 mo sudden cause unknown
17 H S	4	M	NSP Mobitz type I A V LAHB RBBB	NSR, Mobitz type I A V LAHB RBBB day 5	Inserted day 1		Died, ventricular fibrillation day 5
18 A. L.	61	F	NSP Mobitz type II A V LPHB RBBB	CHB 1 hr (rate 45)	Inserted 1 hr	Progressive CHF and shock	Died, day 3 shock
19 P C	11	M	NSR, LAHB PBBB	Mobitz type II A V day 1 CHB (rate 28) day 1 NSR LAHB RBBB day 4	Inserted day 1 removed day 1	Mod. CHF	Alive NSP LAHB RBBB 16 mo
20 F V	80	M	NSR Mobitz type II A V LAHB RBBB	NSP LAHB RBBB day 4 CHB 13 mo	Inserted day 7 removed day 3 permanent demand 15 mo		Alive 3 yr demand pacemaker
21 C E.	6	M	Atrial fibrillation LAHB RBBB	NSP LAHB RBBB day ventricular standstill day 6		CHF	Died day 6 ventricular standstill

Table 1 *Patients with no evidence of 1 V or IBBB on admission*

No	Age	Sex	ECG on admission	A V or I V block	Pacemaker	Complications	Final disposition
1 M B	56	M	Sinus tachycardia	Mobitz type II A V and LBBB day 9 CHB day 3 and ventricular standstill	Day 3 with CHB removed day 15		NSR with LAHB day 6 pacemaker removed day 15 died ventricular standstill day 23
2 K V	69	F	Sinus tachycardia	Mobitz type II A V LAHB and RBBB day 3 CHB day 3	Inserted day 3 with CHB	Pulmonary edema and shock day 3	Died shock day 3
3 G D	69	F	NSR (normal sinus rhythm)	Atrial flutter RBBB day 7 CHB day 7 NSR with I AHB day 9 ventricular standstill day 11	Inserted day 7 with CHB paced as usual day 11	Shock day 9	Died day 20 shock
4 M V	70	M	NSR	Mobitz type II A V day 2 CHB (rate 2s) day 2	Inserted day 2	Shock	Died day 2 shock
5 I H	80	F	NSR LAHB	Intermittent CHB (rate 30) day 1 NSR with LAHB day 2 NSP day 8	Inserted day 1 removed day 14	Pulmonary edema persistent CHF frequent VPS	Alive 14 mo NSR
6 H O S	60	M	NSR LAHB	RBBB with LAHB day 3 LAHB day 4	Inserted day 3	Shock CHB	Died shock and CHB day 10
7 Q H	60	M	NSR combined inferior and anterior MI	Mobitz type I A V day 3 Mobitz type II A V day 4	Inserted day 4	CHI	Alive 4 mo NSR

permanent demand pacemaker. The other died in shock on day 10.

Thus 21 of these 30 patients exhibited IBBB. Ten progressed to CHB six developed ventricular standstill and five showed either no progression or regression of IBBB. The mortality rate in this group was 62 per cent.

Ten patients of all 21 with bilateral bundle branch block were observed to have periods of Mobitz type II A V block. Seven patients developed CHB, one ventricular standstill, and two returned to normal A V conduction during their initial hospitalization. One of these latter two patients developed CHB 18 months later.

Mobitz type II A V block was observed in association with RBBB in six patients and with LBBB in two patients. Its duration was usually a matter of minutes but periods lasting three, six and eight hours were seen.

Of the entire group CHB and ventricular standstill occurred in 21 patients (70 per

cent) during the first seven days. Of the 21 patients who developed CHB or ventricular standstill during the first seven days 16 died—nine in shock and the remaining seven of their arrhythmia.

Recurrent ventricular standstill was observed in four patients who had normal A V conduction but who had previously exhibited CHB. In all four patients intraventricular conduction disturbances (LBBB, IAHB + RBBB, LPIB + RBBB, and LAHB) were noted prior to the recurrent standstill.

Twenty-six patients had pacemaker insertion—13 because of sudden onset of CHB. Seven died in shock and three in ventricular standstill. There was one late death at 23 days (unmonitored) after the temporary pacemaker had been removed. Two patients are alive at 14 and 16 months. Four patients had pacemaker insertion because of sudden ventricular standstill. Two died in shock, one continued in ventricular standstill and could not be paced, one is

Table 11 Patients with LCG evidence of IBBB on admission

No	Age	Sex	ECG on admission	A 1 or I 1 block	Pacemaker	Complications	Final disposition
8 T C	0	M	N R Mobitz type I A 1 RBBB (QRS 0.15 sec)	CHB then ventricular standstill 5 hr			Died ventricular standstill 5 hr
9 S T	63	M	N R LAHB RBBB	CHB (rate 60) day 1	Inserted day 1	Shock	Died day 7 shock
10 J M	64	F	N R Mobitz type I A 1 LAHB RBBB	Ventricular standstill day 4	Inserted day 4	Shock day 8	Died shock day 8
11 D R	53	M	N R LAHB RBBB	Same	Inserted day 1 removed day 14	Mod. CHF	Alive N P LAHB RBBB 4 mo
12 F V	9	F	N R LAHB RBBB	Mobitz type II A 1 day 4 CHB (rate 48) day 5	Inserted day 1 removed day 20		Discharged day 20 CHB asymptomatic (patient) refused pacemaker
13 G H	5	M	N R LAHB RBBB	Ventricular standstill day 1 LAHB day 2	Inserted day 1 removed day 14		Alive LAHB 3 yr
14 F G	80	F	N R LAHB PBBB	Ventricular standstill day 1	Inserted day 2	Intermittent A 1 block day 1	Died ventricular standstill day 2 before pacing could be initiated
15 F P	73	F	N R LAHB RBBB	N R LBBB day 1 Mobitz type II A 1 day 1 ventricular standstill day 1 atrial fibrillation LBBB day 3 N R Mobitz type I A 1 with LBBB day 4	Inserted day 1 removed day 21	Mild CHF	Alive N R Mobitz type I A 1 LBBB 13 mo
16 H M	80	F	N P Mobitz type II A 1 PBBB	CHB day 1	Inserted day 1 permanent (demand) pacemaker 1 mo	Moderate CHF intermittent ventricular tachycardia	Died 8 mo sudden cause unknown
17 H S		M	N R Mobitz type I A 1 LAHB RBBB	N R Mobitz type I A 1 LAHB RBBB day 5	Inserted day 1		Died ventricular fibrillation day 1
18 A P	61	F	N P Mobitz type II A 1 LAHB RBBB	CHB 1 hr (rate 45)	Inserted 1 hr	Progressive CHF and shock	Died day 3 shock
19 P C	6	M	N R LAHB PBBB	Mobitz type II A 1 day 1 CHB (rate 25) day 1 N R LAHB RBBB day 4	Inserted day 1 removed day 1	Mod. CHF	Alive N P LAHB RBBB 16 mo
20 F V	80	M	N R Mobitz type II A 1 LAHB RBBB	N R LAHB RBBB day 1 CHB 18 mo	Inserted day 2 removed day 3 permanent demand 14 mo		Alive 3 yr demand pacemaker
21 C F	67	M	Atrial fibrillation LAHB RBBB	N P LAHB RBBB day 1 ventricular standstill day 6		CHF	Died day 6 ventricular standstill

Table III Patients presenting with RBBB on admission

No	Age	Sex	ECG on admission	AV or IJ block	Pacemaker	Complications	Final disposition
23 C F	78	M	Sinus tachycardia RBBB	CHB (rate 70) day 1		Pulmonary edema	Died CHB day 1
23 M M	76	M	NSR RBBB	CHB ventricular standstill day 1	Inserted day 1	Shock	Died day 1 shock
24 A F	63	M	Sinus tachycardia RBBB	Ventricular standstill day 7		Shock	Died ventricular standstill day 7
25 J M	39	M	Sinus tachycardia RBBB	NSR LAHB RBBB day 3	Inserted day 3 removed day 14	Mild CHF frequent VFS	Alive 6 mo NSR LAHB RBBB

Table IV Patients with LBBB on admission

No	Age	Sex	ECG on admission	AV or IJ block	Pacemaker	Complications	Final disposition
26 M S	76	F	Sinus tachycardia LBBB	CHB (rate 70) day 2 ventricular standstill day 3	Inserted day 2	Mild CHF	Died ventricular standstill day 3 pacemaker failed to function
27 H N	47	F	NSR LBBB	CHB day 2 (rate 60)	Inserted day 2		Died day 2 shock
28 S L	67	M	NSR LBBB	CHB day 1 (rate 30)	Inserted day 1	Shock	Died shock day 1

alive at 13 months. Nine patients had pacemaker insertion as a prophylactic measure because of recognition of RBBB or one of the patterns of IBBBB. Three of these patients died—one in shock, one in ventricular fibrillation, and one at 8 months with a functioning permanent pacemaker (arrhythmia is a likely cause of death). Two patients progressed to either CHB or ventricular standstill within the first hospital week and are still alive at 4 months and 24 months. The four patients who did not develop CHB or ventricular standstill during their initial hospitalization are alive at 4, 4, 6 and 18 months.

Complications encountered during pacemaker insertion included multiple ventricular premature systoles and episodes of ventricular tachycardia. These were all promptly treated and were not thought to influence the patient's subsequent course.

Postmortem examinations revealed extensive acute anteroapical infarction. In one patient old posterior wall infarction was

also noted. Detailed studies of the conduction pathways were not performed.

Discussion

In our group of patients 76 per cent of those who showed a pattern of IBBBB progressed to either CHB or ventricular standstill. This high incidence has been noted by others.^{4,11,12} The most common manifestation of IBBBB leading to these complications has been RBBB + LAHB.^{11,12} Mobitz type II A V block has been noted occasionally to be a precursor of CHB in acute anterior wall myocardial infarction.¹³

Ten of our patients (33 per cent) had periods of Mobitz type II A B block. Seven of these patients developed CHB or ventricular standstill within the first week. One developed complete heart block on day 25 and another at 18 months. Thus, a total of 90 per cent of these patients required a pacemaker following the recognition of Mobitz type II A V block.

The question of prophylactic pacemaker

Table 1 Patients with CHB on admission

No	Age	Sex	ECG on admission	A V or I V block	Pacemaker	Complications	Final disposition
21 T	50	M	1st CHB (rate 70)		Inserted day 1 permanent demand pacemaker inserted 1 mo	Mild CHF	Alive permanent demand pacemaker 14 mo
30 J h	59	F	1st CHB (rate 69)	1st LAMB BBBB day ventricular standstill day 3	Inserted day 1 pacemaker responded	CHF shock	Died day 10 shock

insertion once these patterns are recognized remains unsettled. Godman and colleagues⁴ who recognized the high mortality rate of bilateral bundle branch block concluded that the serious risk of electrode insertion was not warranted because of the small potential gain. Roos and Dunning¹⁷ describe prophylactic pacemaker insertion in ten patients with IBBBB pattern. Although CHB and ventricular standstill were treated, the death rate remained high because of cardiogenic shock. Scanlon and co-workers¹⁸ observed a slightly better prognosis. They felt that insertion of a prophylactic pacemaker was indicated because it did improve prognosis.

Temporary pacemakers were inserted in 86 per cent of our patients (26 patients). The mortality rate of this group was 61 per cent. The major factor contributing to death was the severity of myocardial infarction as manifested by the high incidence of cardiogenic shock and refractory congestive heart failure. This experience has been noted by others.¹⁹ Pacemaker therapy was thought to contribute to the management of patients less severely ill by facilitating the management of heart failure and supra-imposed serious ventricular arrhythmias and by preventing recurrent ventricular standstill.

There were four patients who did not have pacemakers inserted because IBBBB patterns were not recognized; all four died in CHB or ventricular standstill. One may speculate as to the probable benefit of pacing and their course was not complicated by shock or congestive heart failure.

One of the questions raised by this study is when to remove a temporary pacemaker.

Patient No. 1 died suddenly and unexpectedly on day 23. This patient presented with IBBB and progressed to CHB. His temporary pacemaker was removed nine days after IBBB disappeared. Although this represented only one example of sudden and unexpected death in a group of three with IBBB and transient CHB, the larger experience of Atkins and associates¹¹ would suggest a more significant mortality rate. Further studies are clearly indicated to determine the need for permanent pacemaker implantation.

It is concluded from this study that insertion of a temporary electrode catheter is warranted in all patients with acute anterior wall myocardial infarction who show evidence of IBBBB. Although the length of time the pacemaker should remain in place is not clear, it is our practice to maintain this catheter in position for 21 days unless this is prohibited by complications produced by the catheter.

It is hoped that more sophisticated studies utilizing His bundle recording will assist in determining the time of temporary catheter removal and necessity of permanent pacemaker implantation.

Summary

Thirty patients with incomplete bilateral bundle branch block (IBBBBB) or atrioventricular (A V) block complicating acute anterior wall myocardial infarction are discussed. The hospital mortality rate of this group was 63 per cent. Of patients who developed IBBBB, 76 per cent progressed to either complete heart block, ventricular standstill or ventricular fibrillation. Findings that are stressed are the high incidence

of Mobitz type II A V block and recurrence of life threatening arrhythmias. It is concluded that a temporary electrode catheter is warranted in this group of patients.

REFERENCES

- 1 Norris R M Heart block in posterior and anterior myocardial infarction *Br Heart J* 31:352 1969
- 2 Lissers B W and Julien D G Artificial pacing in management of complete heart block complicating acute myocardial infarction *Br Med J* 2:142 1968
- 3 Friedberg C K Donoso I and Stein W G Nonsurgical acquired heart block *Ann N Y Acad Sci* 111:835 1964
- 4 Codrion M J Lissers B W and Julien D C Complete bundle branch block complicating acute myocardial infarction *N Engl J Med* 282:237 1970
- 5 Meyers G B Klein H A and Stofer B E I Correlation of electrocardiographic and pathologic findings in anteroapical infarction *Am Heart J* 36:535 1948
- 6 Meyers G B Klein H A and Horvitz T H Correlation of electrocardiographic and pathologic findings in large anterolateral infarcts *Am Heart J* 36:838 1948
- 7 Criteria Committee of the New York Heart Association Diseases of the heart and blood vessels ed 2 Boston 1964 Little Brown & Company
- 8 McNally E M and Benchimol A Medical and physiologic considerations in the use of artificial cardiac pacing *J Am Heart J* 75:380 1968
- 9 Langendorf K and Pick A Atrioventricular block type II (Mobitz)—Its nature and clinical significance (editorial) *Circulation* 38:819 1968
- 10 Narula O S Scherling B J Simet I and Javier R P Atrioventricular block—I: definition and classification by His bundle recording *Am J Med* 50:146 1971
- 11 Ross J C and Dunning A J Right bundle branch block and left axis deviation in acute myocardial infarction *Br Heart J* 3:817 1970
- 12 Scullion P J Pryor K and Blount G S Right bundle branch block associated with left superior or inferior intraventricular block *Circulation* 42:1135 1970
- 13 Stock R J and Mcken D I Observations on heart block during continuous electrocardiographic monitoring in myocardial infarction *Circulation* 38:993 1968
- 14 Atkins J M Ichim S J Blomquist G and Mullins C B Indications of right bundle branch block and left anterior hemiblock. A new indication for permanent pacing (abst) *Am J Cardiol* 26:674 1970

Left anterior hemiblock and right bundle branch block before and after surgical repair of tetralogy of Fallot

Elliot Chesler MD (Rand) FRCP (Edin) FACC

Walter Beck MSc MMed MRCP FICC

Ischa Schrire MSc PhD MD FRCP FRCP FICC†

Cape Town South Africa

Recently the occurrence of left anterior hemiblock and right bundle branch block (RBBB) has been reported following total surgical correction of tetralogy of Fallot.¹⁻⁴ This complication is related to surgical damage of the anterior branch of the left bundle as well as to damage of the right bundle of the conducting system which are in close relationship to the posterior margin of the ventricular septal defect.^{1,2}

In the presence of RBBB when the mid vector points to the left at -30° or more the postoperative electrocardiogram (ECG) resembles that of endocardial cushion defect. It is of interest that RBBB and the combination of left anterior hemiblock (LAH) and RBBB have also been described in the preoperative ECG of patients with tetralogy of Fallot.^{3,4} Also it has been pointed out that when the ECG shows severe right ventricular hypertrophy the typical findings of LAH may be obscured by the presence of marked right axis deviation and only the initial 0.02 second vector may indicate the presence of a minor degree of left conduction abnormality.³ Disagreement appears to exist however as to the

frequency with which the 0.02 second vector is disturbed in LAH.³

In our surgical experience with cases of tetralogy of Fallot we have found LAH and RBBB to occur in 7 per cent of cases postoperatively. The purpose of this paper is to determine the incidence of these conduction abnormalities preoperatively and also to determine whether minor evidence of LAH in the presence of right ventricular hypertrophy and right axis deviation predisposes to the subsequent development of LAH and RBBB or even complete heart block.

Materials and methods

Our material consists of 217 patients who were operated on for complete correction of tetralogy of Fallot. One hundred and thirty three were male and 84 were female and their average age was 10 years. All patients were fully investigated by cardiac catheterization and angiography. This series does not include patients with tetralogy complicated by other malformations such as atrial septal defect, endocardial cushion defect or unusual types of ventricular septal defect. Of the 217 operations 184 (85)

From the Cardio-Pulmonary Unit, Groote Schuur Hospital, Department of Medicine, University of Cape Town and the Cardiovascular Pulmonary Research Group.

Supported by the Department of Medicine by the South African Medical Research Council.

Received for publication Oct. 8, 1971.

Reprint request to Dr. Elliot Chesler, Cardio-Pulmonary Research Group, Department of Medicine, Groote Schuur Hospital, Cape Town, South Africa.

Dr. Schrire died Feb. 16, 1972.

Table I Conduction abnormalities before surgery in 217 cases of tetralogy of Fallot (Group I)

Diagnosis	No of patients	% of patients
Complete RBBB*	0	0
L AH†	0	0
Incomplete RBBB alone	22	10
Minor L AH	12	10
Minor L AH with incomplete RBBB	10	
Total incomplete RBBB	32	14.7

*RBBB = right bundle branch block

†L AH = left anterior hemiblock

per cent) were performed by one surgeon, and in all cases the ventricular septal defect was described as being infracristal and of the usual size.

Twelve lead ECGs were available in all 217 patients preoperatively and in 160 of these ECGs were also available after operation. The latter tracing was available for examination at a mean interval of 17 months following operation. In the remaining 57 patients only rhythm strips were available in the postoperative period.

The material is divided into two groups.

Group 1 The entire group of 217 patients was used to analyze the conduction abnormalities preoperatively in uncomplicated cases of tetralogy of Fallot and to ascertain the incidence of postoperative complete heart block.

Group 2 The conduction abnormalities induced by surgery were analyzed in 160 of the 217 cases where both pre and post operative tracings were available.

Criteria for conduction abnormalities Criteria for the diagnosis of conduction abnormalities were as follows:

1 **Left anterior hemiblock** This was diagnosed when the mean QRS axis was deviated to the left at -30° or more. Particular attention was paid to the location of the 0.02 second vector in these cases.

2 **Right bundle branch block** QRS duration of 0.12 sec or more with a prominent S wave in standard Lead I and RSR in V_1 . Incomplete RBBB was considered to

Table II Conduction abnormalities induced by surgery in 160 cases of tetralogy of Fallot (Group II)

Diagnosis	No of patients	% of patients
L AH*	0	0
L AH with RBBB†	11	7
Complete RBBB	120	75
Incomplete RBBB	4	2.5
Total RBBB	135	84

*L AH = left anterior hemiblock

†RBBB = right bundle branch block

Table III Relationship of preoperative minor left anterior hemiblock to postoperative left anterior hemiblock in 160 patients

Preoperative conduction defect	No	Postoperative L AHB* (No cases)	% developing L AHB
Minor L AHB	16	5	31
No L AHB	144	6	4
Total	160	11	7

*L AHB = left anterior hemiblock

be present when the QRS duration was 0.10 to 0.11 sec. The majority of our patients were in the 7 to 10 year age group at which time the QRS duration is usually between 0.07 to 0.09 sec.¹⁰

3 **Left anterior hemiblock and right bundle branch block** In the presence of RBBB three main vectors were plotted in the frontal plane from the scalar ECG according to the method of Grant.¹¹ The first vector was plotted for the first 0.0 sec, the second for the intermediate portion and the third for the last 0.04 sec. L AH was considered to be present when the mid vector was located at -30° or further leftward. In these cases as shown by Rosenbaum,¹ the QRS forces at 0.02 sec are located at $+120^\circ$ in the frontal plane and produce small q waves in Leads I and V_1 and small r waves in Leads II and III. In the next 0.04 sec the mid vector points to the left at -30° or more, resulting in

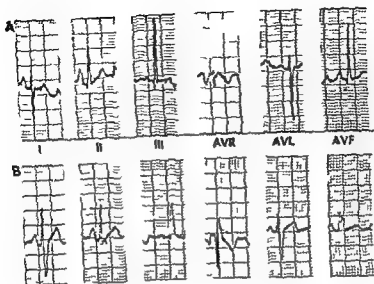


FIG. 1. ECG's showing change usually observed in tetralogy of Fallot. A: Preoperative tracing shows right axis deviation. B: Postoperative tracing showing complete RBBB. There is no evidence of LAH in either tracing.

deep S waves in standard Leads II, III and aVF. The terminal forces resulting from RBBB point to the right at about $+180^\circ$.

4. *Minor left anterior hemiblock*. This was considered to be present when in the presence of ECG evidence of severe right ventricular hypertrophy and marked right axis deviation, small q waves were present in standard Leads I and aVL associated with an rSR wave in Lead III and an rS or rSR wave in Lead II. In the presence of RBBB this abnormality was similarly diagnosed when the first vector was located at $+120^\circ$ but without deviation of the mid vector to the left beyond -30° .

Results

Preoperatively, in Group 1 right axis deviation was present in 213 of the 217 cases and the mean QRS axis was found to be $+150^\circ$. In the remaining 4 cases the QRS axis was normal. The conduction abnormalities are detailed in Tables I and II. Complete RBBB and LAH and the combination of these abnormalities were universally absent in the preoperative tracings. Incomplete RBBB was infrequent and occurred in 7 per cent of the cases and a minor degree of LAH was present in 10 per cent of the cases.

Postoperatively, in Group 1 RBBB oc-

curred in 84 per cent of the cases (Fig. 1) and the combination of LAH and RBBB occurred in 7 per cent of the cases. Of the 16 patients with a minor degree of LAH preoperatively, 5 (32 per cent) developed LAH after operation (Fig. 2). In the remaining 11 cases the mid vector displayed a slight leftward shift but not beyond -30° (Fig. 3). Of the 144 patients who had no evidence of LAH at all before operation, only 6 (4 per cent) developed LAH. Of these 6 with postoperative LAH, 3 developed a pattern without Q waves in Leads I and aVL; the major QRS forces however were deviated in a pattern quite typical of LAH (Fig. 4). Evidence of LAH was thus present preoperatively in 5 of the 11 patients with surgically induced LAH.

Complete heart block followed surgery in 2 of the 217 patients. Neither patient had evidence of preoperative LAH. In one case, heart block was evident immediately following completion of the operation and has persisted for 7 years without Stokes-Adams attacks. In the second case, complete heart block occurred intermittently after operation; subsequently there was a return to sinus rhythm with ECG evidence of LAH and complete RBBB. This patient was recatheterized one year after surgery and during this procedure again developed temporary complete heart block. Sinus

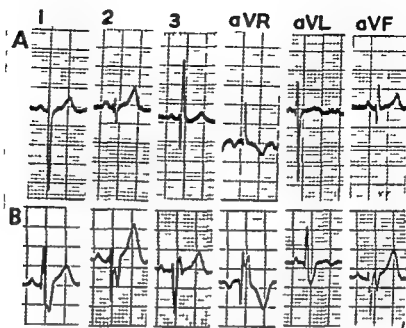


Fig 2 ECG showing *A* preoperative evidence of minor LAH in the presence of RAD. The small *q* waves present in Leads I and *aVL* and the small *r* waves in Leads III and *aVF* indicate the 0.02 sec located at +120°. Postoperatively the degree of LAH has increased with the mid vector located at about -100° in the presence of complete RBBB.

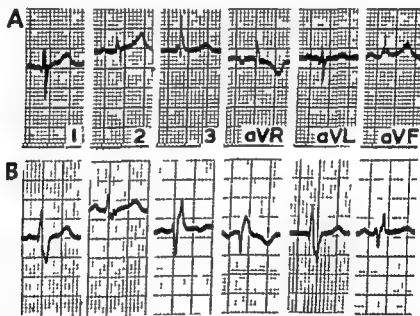


Fig 3 ECGs showing *A* preoperative evidence of a minor degree of LAH in the presence of right axis deviation and *B* postoperative tracing indicating complete RBBB. The deeper S wave in *S₁* and the taller R waves in *aVL* and *S₂* indicate a slight leftward shift of the mid vector but not beyond -30°.

rhythm then returned with evidence of LAH and complete RBBB. Six years after operation complete heart block returned spontaneously and has remained as a permanent feature. The occurrence of Stokes-Adams attacks then necessitated implantation of a permanent transvenous pacemaker which has been utilized for the last three years.

Commentary

Cases of tetralogy of Fallot with severe obstruction to pulmonary blood flow usually exhibit right axis shift of the mean QRS axis. Thus Keith¹² (who studied 62 cases) and Burch and DePasquale¹⁴ who studied 92 cases) found that all their cases showed marked to moderate right axis deviation. A normal axis may be encountered

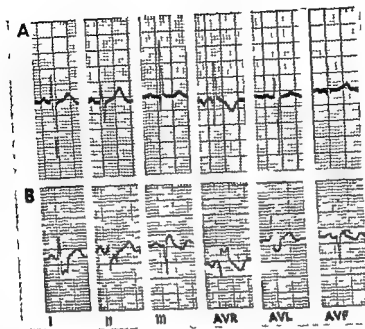


Fig. 4 ECGs showing *A* preoperative right axis deviation without evidence of minor LAH *B* Postoperative tracing shows complete RBBB and LAH. There are no Q waves in Leads I and aVL, indicating absence of a significant disturbance of 0.02 second vector.

in cases with less obstruction to pulmonary blood flow but left axis deviation (LAH) is extremely rare and has a tendency to be associated with the pentalogy (tetralogy of Fallot with patent foramen ovale)¹⁵ We have also encountered cases of pentalogy and cases of tetralogy with endocardial cushion defect with LAH but these cases have been excluded from the present series. In an analysis of 136 patients with tetralogy, Kulbertus, Coyne and Halliday Smith² found that 3 cases (2.2 per cent) manifested LAH. In one of these cases the infracristal defect was unusually large and in the other two cases there were associated anomalies such as multiple muscular ventricular septal defects (VSDs), an abnormal tricuspid valve, secundum atrial septal defect and rupture of a sinus of Valsalva. These authors also found LAH and RBBB in a further 7 cases (5.2 per cent). In only one of these cases was the VSD of the usual infracristal variety; in the remaining cases there was an endocardial cushion type of VSD, multiple muscular VSDs, or left ventricular-right atrial communication. In our series of 214 cases of uncomplicated cases of tetralogy with the usual infracristal type of VSD, the ECG was characterized

by the absence of LAH, RBBB and LAH combined with RBBB.

It is apparent that in the uncomplicated form of tetralogy of Fallot, LAH, RBBB and LAH with RBBB are rare and that the presence of these conduction abnormalities indicates an unusual type of VSD or an additional malformation. Recently Rosenbaum and associates⁴ in their analysis of the ECG features of four patients with tetralogy of Fallot who developed postoperative LAH and RBBB pointed out that in the presence of severe right ventricular hypertrophy and right axis deviation, small q waves in standard Leads I and aVL, and small initial r waves in Leads II, III, and aVF are unusual and may possibly indicate the presence of a minor degree of LAH. These findings have been in keeping with their previous observations that in the presence of severe right ventricular hypertrophy, a small degree of LAH does not produce main QRS forces superiorly and to the left but instead only produces initial forces inferiorly to the right when there is marked right axis deviation.¹² In LAH, the QRS forces for the first 0.02 sec (which are orientated at approximately +120° in the frontal plane)

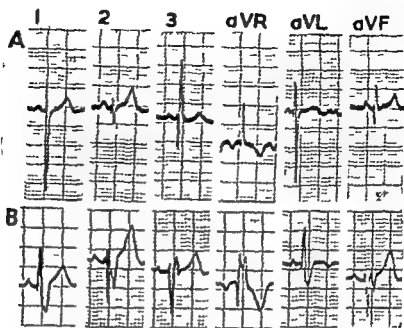


Fig 2 ECG showing *A* preoperative evidence of minor LAH in the presence of RAD. The small q waves present in Leads I and aVL and the small r waves in Leads III and aVF indicate the QRS located at $+120^\circ$. To top right the degree of LAH has increased with the mid vector located at about -100° in the presence of complete RBBB.

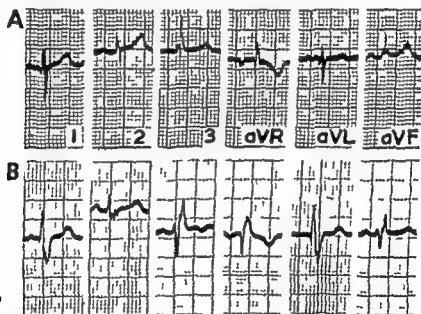


Fig 3 ECGs showing *A* preoperative evidence of a minor degree of LAH in the presence of right axis deviation and *B* postoperative tracing indicating complete RBBB. The deeper S wave in S_2 and the taller R wave in aVL and S_1 indicate a slight leftward shift of the mid vector but not beyond -30° .

rhythm then returned with evidence of LAH and complete RBBB. Six years after operation complete heart block returned spontaneously and has remained as a permanent feature. The occurrence of Stokes-Adams attacks then necessitated implantation of a permanent transvenous pace maker which has been utilized for the last three years.

Commentary

Cases of tetralogy of Fallot with severe obstruction to pulmonary blood flow usually exhibit right axis shift of the main QRS axis. Thus Keith¹³ (who studied 67 cases) and Burch and Del'isquale¹⁴ (who studied 92 cases) found that all their cases showed marked to moderate right axis deviation. A normal axis may be encountered

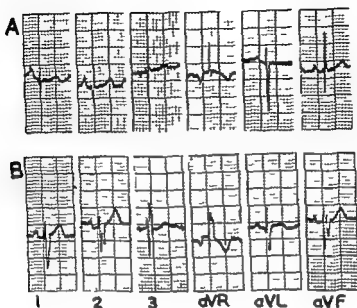


Fig 6 ECG showing *A* preoperative minor LAH and right axis deviation *B* Postoperative complete RBBB and shift of mid vector to the left typical of LAH

Dispute thus exists about the frequency of disturbance of the 0.02 second vector in LAH. Our findings would indicate (even though the numbers are small) that the 0.02 second vector is usually disturbed and that when this finding is present preoperatively in the presence of marked right ventricular hypertrophy and right axis deviation there is an increased tendency to the development of LAH.

The risk of developing LAHB following surgery is small (7 per cent) findings which are in agreement with those of Kulbertus, Coyne, and Haldie Smith.² The prognosis for these patients will be answered by long term follow up since it is known that when LAH and RBBB are a result of ischemic heart disease or a sclero-degenerative process there is a strong tendency to develop complete heart block subsequently.^{14,15} Our one patient who developed intermittent complete heart block then LAH and RBBB and finally stable complete heart block almost certainly had damage to the common bundle or the inferior division of the left bundle at the time of operation. Immediate postoperative complete heart block occurred in less than 1 per cent of our cases and this experience is in accord with other series.¹⁶

Summary

The preoperative ECG was studied in 217 patients who underwent total surgical correction of uncomplicated tetralogy of Fallot and the effects of surgery were observed in 160 of these cases. Analysis of the incidence of LAH, RBBB and the combination of these conduction defects revealed that these were universally absent in the preoperative tracings; their presence should therefore suggest the possibility of an unusual variety of VSD or an associated malformation. RBBB was induced surgically in 84 per cent and the combination of RBBB and LAH was induced surgically in 7 per cent of cases. In LAH the mid vector was located at -30° or further to the left and in the majority of cases the 0.02 second vector was located at $+120^\circ$ producing M waves in Leads I and aVL. Preoperatively 10 per cent of the tracings showed the presence of small q waves in Leads I and aVL in the presence of right axis deviation (RAD) and it has been previously suggested that this represents a minor degree of LAH. Our data would lend credence to this possibility because surgically induced LAH occurred in 31 per cent of these cases and in only 4 per cent of the cases where these findings were absent. In the patients

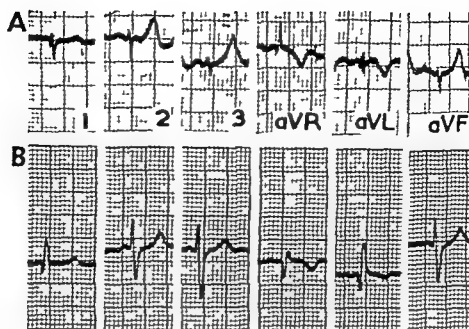


Fig 5 LCG showing *A* preoperative minor LAH in the presence of marked right RAD mean QRS axis about $+210^\circ$ *B*, Postoperative tracing shows LAH with mean QRS vector about -40°

are a result of early activation of the posteroinferior wall of the left ventricle in an inferior and rightward direction and are responsible for the Q waves in Leads I and aV_L .

These features were looked for in the preoperative ECG of our patients and found in 10 per cent of our tracings in the presence of right axis deviation. One third of these patients subsequently developed LAH and RBBB with the mid vector then located to the left of -30° whereas this complication occurred in only 4 per cent of patients whose ECGs showed no evidence of hemiblock at all. These findings would lend support to Rosenbaum's observations.

Feldt, DuShane, and Titus⁸ in their study of the anatomy of the conduction system in the tetralogy of Fallot found that 5 of their 78 autopsied cases of tetralogy had an ECG considered to be similar to that of the AV canal pattern. This similarity lay in the fact that the initial QRS axis was directed inferiorly and to the right with Q waves in Lead I and aV_L producing an initial counterclockwise loop with a mean QRS axis of -150° .⁸ In all these patients the VSD was of the usual infracristal type and it was noticed that there was a short distance between the AV node and the left bundle branches; the effect of surgery on the ECG was not studied. This ECG pattern is compatible with a minor

degree of LAH as encountered in some of our cases (Fig 5) but usually in our case the mean QRS axis did not deviate as far to the right (Fig 6).

It would appear therefore, that typical LAH is rare but that a minor degree of LAH in the presence of right axis deviation (RAD) may occur in uncomplicated tetralogy of Fallot and that following surgery in this type of case, the degree of hemiblock may increase postoperatively, and the mean QRS forces may then point to the left. The precise anatomy of the conduction system in these cases is not known but presumably the anterior division lies unusually close to the VSD so that surgery further damages the conduction tissues.

Lemberg, Castellanos, and Arcebal⁹ have recently observed that in LAH and RBBB the initial 0.02 second vector may be oriented to the left and superiorly and they have attributed this to myocardial and septal fibrosis findings which are in disagreement with those of Rosenbaum. In 4 of our 11 patients whose postoperative ECGs were otherwise compatible with LAH there was also no significant disturbance of the 0.02 second vector and Q waves were absent in Leads I and aV_L (Fig 4). This may possibly be a result of septal fibrosis, significant postoperative septal rotation, or even a minor degree of left posterior hemiblock.

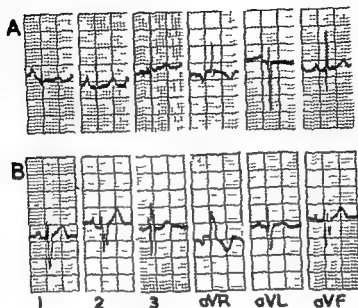


Fig. 6 ECGs showing *A* preoperative minor LAH and right axis deviation *B* Postoperative complete PBBB and shift of QRS vector to the left typical of LAH

Dispute thus exists about the frequency of disturbance of the 0.02 second vector in LAH. Our findings would indicate (even though the numbers are small) that the 0.02 second vector is usually disturbed and that when this finding is present preoperatively in the presence of marked right ventricular hypertrophy and right axis deviation there is an increased tendency to the development of LAH.

The risk of developing LAHB following surgery is small (7 per cent) findings which are in agreement with those of Kulbertus, Coyne and Halliday-Smith.² The prognosis for these patients will be answered by long term follow up since it is known that when LAH and RBBB are a result of ischemic heart disease or a sclero-degenerative process there is a strong tendency to develop complete heart block subsequently.^{11,12} Our one patient who developed intermittent complete heart block then LAH and RBBB and finally stable complete heart block almost certainly had damage to the common bundle or the inferior division of the left bundle at the time of operation. Immediate postoperative complete heart block occurred in less than 1 per cent of our cases and this experience is in accord with other series.¹³

Summary

The preoperative ECG was studied in 217 patients who underwent total surgical correction of uncomplicated tetralogy of Fallot and the effects of surgery were observed in 160 of these cases. Analysis of the incidence of LAH, RBBB and the combination of these conduction defects revealed that these were universally absent in the preoperative tracings their presence should therefore suggest the possibility of an unusual variety of VSD or an associated malformation. RBBB was induced surgically in 84 per cent and the combination of RBBB and LAH was induced surgically in 7 per cent of cases. In LAH the QRS vector was located at -30° or further to the left and in the majority of cases the 0.02 second vector was located at $+120^\circ$ producing q waves in Lead I and aV_L . Preoperatively 10 per cent of the tracings showed the presence of small q waves in Leads I and aV_L in the presence of right axis deviation (RAD) and it has been previously suggested that this represents a minor degree of LAH. Our data would lend credence to this possibility because surgically induced LAH occurred in 31 per cent of these cases and in only 4 per cent of the cases where these findings were absent. In the patients

with surgically induced IAH, evidence of a minor degree of IAH was present in half of these cases before operation

REFERENCES

- 1 Lindman B and Wolf M D Total correction of tetralogy of Fallot Changes in the electrocardiogram following surgery *Circulation* 31:391 1965
- 2 Kulbertus H J Coyne J J and Halliday Smith K A Conduction disturbance before and after surgical closure of ventricular septal defect *Am Heart J* 77:123 1969
- 3 Roembum M B Corrado G Oliveri R Castellanos A and Lazzari M V Right bundle branch block with left anterior hemiblock surgically induced in tetralogy of Fallot Relation to the mechanism of electrocardiographic changes in endocardial cushion defect *Am J Cardiol* 26:112 1970
- 4 Scanton P J Pryor R and Blount S G Right bundle branch block associated with left superior or inferior intraventricular block Clinical setting prognosis and relation to complete heart block *Circulation* 32:1123 1965
- 5 Gruen H C and Bishop J K Conduction system in human heart with interventricular septal defects *J Thorac Cardiovasc Surg* 33:421 1958
- 6 Lev M The architecture of the conduction system in congenital heart disease II Tetralogy of Fallot *Arch Pathol* 67:572 1959
- 7 Lev M Conduction system in congenital heart disease *Am J Cardiol* 21:619 1968
- 8 Eldit K H DuShane J W and Titus J I The anatomy of the atrioventricular conduction system in ventricular septal defect and tetralogy of Fallot Correlation with the electrocardiogram and vectorcardiogram *Circulation* 31:771 1966
- 9 Lemberg I Castellanos A and Arcebal A G The vectorcardiogram in acute left anterior hemiblock *Am J Cardiol* 28:183 1971
- 10 Jerrer M J The excitation syndrome Mechanisms and treatment in Breast A N editor *Cardiovascular clinics vol 3 Arrhythmias Philadelphia 1970 F A Davis Company p 2*
- 11 Grant R P Clinical electrocardiography New York 1957 McGraw Hill Book Co Inc p 18
- 12 Rosenbaum M H Lazzari M V and Lazzari J O Los hemibloques Buenos Aires 1968 Puckett
- 13 Keith J D Rowe P D and Ward I Heart disease in infancy and childhood New York 1967 The Macmillan Co p 614
- 14 Burch G I and Delisquaire N P Electrocardiography in the diagnosis of congenital heart disease Philadelphia 1967 F E & T Leiber p 361
- 15 Cavalet R M Richmond J B and Berkower C A Case of tetralogy of Fallot with patent foramen ovale (pentacody) showing a marked left ventricular hypertrophy and left axis deviation *J Pediatr* 35:115 1949
- 16 Lasser R P Hift J I and Friedberg C K Relationship of right bundle branch block and marked left axis deviation (with left parietal or perinfection block) to complete heart block and syncope *Circulation* 37:129 1968
- 17 Lemberg J Etiology and pathology of bilateral bundle branch block in relation to complete heart block *Progr Cardiovasc Dis* 6:409 1964
- 18 Lepeschkin F The electrocardiographic diagnosis of bilateral bundle branch block in relation to heart block *Progr Cardiovasc Dis* 6:145 1964
- 19 McCoom D C Omsley P A DuShane J W and Kirklin J W Surgical induced heart block *Ann N Y Acad Sci* 118:30 1961

Experimental and laboratory reports

Exchangeable potassium in heart disease Long-term effects of potassium supplements and amiloride

M S Crowson MB MRICP
J M Neutze MD FRACP
M B John BSc
Auckland New Zealand

There is general agreement that body potassium is reduced in patients with severe heart disease particularly when this is complicated by heart failure and the use of powerful potassium wasting diuretics. While some workers believe that potassium depletion reflects loss of lean body mass alone others suggest that cellular depletion is also present.

In an earlier study from this hospital Singh Hurley and North¹ compared values of total exchangeable potassium (K_e) in patients with heart disease with values from normal subjects reported in the literature. They found that patients on diuretics had low values of K_e expressed as mEq K_e/kg body weight (mEq of exchangeable potassium per kilogram of body weight) although all were on potassium supplements or spironolactone. In a short term study they showed that the addition of the potassium sparing diuretic amiloride 20 mg daily to furosemide 80 mg daily resulted in a 33 per cent reduction in urinary loss of potassium.

These observations have been extended

in the present study which had two primary aims: (1) to compare the K_e of control patients with heart disease who were not on diuretics with that of trial patients who were on diuretics and an potassium supplements and (2) to compare the relative efficacy of potassium supplements and amiloride in maintaining K_e over a relatively long period.

Methods

Exchangeable potassium (K_e) was measured by isotope dilution using ⁴²K following the method of Fleck and associates² who recommended a period of 24 hours for equilibration. The tracer was given orally and after 24 hours the specific activity of four urine specimens passed at hourly intervals was measured in a Packard twin channel autogamma spectrometer. Chemical measurements of serum and urinary potassium were made with an internal standard flame photometer. No allowance was made for fecal loss of potassium which is generally less than 0.5 per cent of the administered dose.³ The mean of the four

From the Cardiology Department, George Lane Hospital, and the Respiratory Unit, Auckland Hospital, Auckland, New Zealand.

Received for publication: August 25, 1972.

Revised for publication: Dr J M Neutze, Cardiology Department, George Lane Hospital, Green Lane West, Auckland, New Zealand.

Table 1 Comparison of control and trial patients

Patient No	Control patients							Trial patients					
	Age (yr)	Sex	Wt (kg)	Diagnosis	NH	Ke/LBM (mEq/kg)	Serum K ⁺ (mEq/l)	Patient No	Age	Sex	Wt (kg)	Diagnosis	NH
1	47	M	63.5	AVD*	2	60.5	4.9	1	59	F	80.0	MVD	3
2	49	M	69.0	IHD*	4	5.5	4.0	2	43	F	73.7	AVD	4
3	20	M	76.5	AVD	3	6.5	4.0	3	53	F	58.6	MVD	3
4	01	M	67.5	IHD	4	51.9	3.9	4	56	M	51.7	AVD	3
5	55	F	51.7	AVD	3	60.5	3.8	5	66	M	78.1	MVD	3
6	40	M	67.1	IHD	4	6.5	3.9	6	44	F	55.3	MVD	3
7	46	M	72.1	IHD	4	51.5	4.9	7	66	F	69.7	MVD	4
8	49	M	64.5	AVD	3	5.5	4.4	8	67	M	67.9	MVD	3
9	43	M	69.6	IHD	4	—	3.9	9	28	F	61.5	AVD	4
								10	51	F	55.4	MVD	3
								11	35	F	54.1	MVD	3

*Abbreviations: AVD = aortic valve disease; IHD = ischemic heart disease; MVD = mitral valve disease; NH = New York Heart Association classification. Details of serum K⁺ and Ke/LBM values for trial patients are shown in Table IV.

estimates of Ke was taken for each patient, the average deviation from the mean value for individual estimates being 3.9 per cent (SD = 3.3 per cent). Results were accepted only if serial estimates showed that equilibrium had been reached and results were excluded from one patient who did not reach equilibrium.

The expression mLq Ke/K_b body weight does not make adequate allowance for the loss of lean body mass in disease states. For this reason Ke is expressed in this study as mLq Ke/Kg lean body mass. This expression has the advantage that it also allows for the difference in fat mass between males and females.

Total body water (TBW) was measured by the sampling of both urine and plasma five hours after an oral dose of 500 μ Ci of tritiated water. Samples were assayed in a Packard liquid scintillation spectrometer. Values of TBW calculated from urine and plasma samples showed good correlation ($r = 0.91$), and the average of the two values was used for all calculations. Lean body mass (LBM) was calculated from the

formula $LBM = \frac{TBW}{1.1} \times 0.73$ per cent⁴

Red cell potassium (K_{RBC}) was measured by the method of Singer and colleagues.⁵ Blood urea, serum sodium, CO₂ content, creatinine, uric acid, one hour postprandial

blood glucose, bilirubin, SGOT, and alkaline phosphatase were measured with a Technicon autoanalyzer. Normal values for uric acid in our laboratory are: Females = 3.2 to 7.2 mg per cent; Males = 3.7 to 8.3 mg per cent. For comparison K_{RBC} and serum potassium were measured in 50 normal staff members. The mean value of K_{RBC} for this group was 97.2 mEq per liter (SD = 4.6 mLq per liter); the value for males was 94 mLq per liter and for females 98.4 mLq per liter. The mean value for serum potassium was 4.2 mLq per liter (SD = 0.3 mEq per liter).

Patients

There were nine control patients, eight of whom were men. Five of these patients had ischemic heart disease and four had valvular disease. One patient only was receiving digitalis and two patients were taking propranolol. There were eleven trial patients, eight of whom were women. All had severe valvular disease and ten were on treatment with digitalis, furosemide 80 mg, and potassium supplements 48 mEq daily given as potassium chloride (Slow K). One patient (No. 5) was on digitalis, furosemide 40 mg, and potassium chloride 32 mEq daily. All patients were on this therapy for a minimum of three months before the start of the trial, the mean period being 2.1 years.

11 mcf 84
A mbe 1

Table II Comparison of control and trial patients (mean values)

	No of patients	Age (yr)	Ht (kg)	Dietary K (mEq/kg)	TBW/Wt (%)	Serum K ⁺ (mEq/L)	Ke/LBM† (mEq/kg)	Serum Na ⁺ (mEq/L)	Serum creatinine (mg %)	Uric acid (mg %)
Control	8	43	67.1	51	61	4.0	5.8	137	1.2	8.4
Trial	11	51	63.1	48	58	3.9	51.6	140	1.1	9.5

TBW = total body wt

† LBM = lean body mass

‡ Difference between control and trial patients = 0.05 > P > 0.01

§ Does not include potassium supplement

The two groups were well matched for symptomatic limitations dietary intake of potassium body weight and lean body mass. Age distribution was similar and no patient was obese.

Design of study

Comparison of control and trial patients (Tables I and II). Ke/kg lean body mass, serum potassium, K₂O, and other biochemical values were measured in control patients (not on diuretics) and in trial patients (on diuretics and potassium supplements).

Comparison of the efficacy of potassium supplements and amiloride in maintaining Ke in trial patients. For two months after the initial measurements trial patients were maintained on furosemide and potassium supplements and measurements were repeated at the end of this period. Amiloride was then substituted for potassium supplements. Three patients were given 15 mg daily for two weeks and then changed to 10 mg daily and the remaining eight patients were given 10 mg daily from the outset. Two months later measurements were again repeated. Dietary potassium, clinical status, body weight, skin fold thickness and biochemical indices were recorded at intervals throughout the study. Differences between control and trial groups were assessed by the unpaired *t* test and changes throughout the study in the trial group were assessed by the paired *t* test.

Results

Comparison of control and trial patients (Table II). The mean value for Ke in control patients was 57.9 mEq/kg lean body mass (LBM). This is comparable with

Table III Stability of trial patients (mean values)

Study period	Mean body wt (kg)	Mean lean body mass (kg)
1	63.5	50.4
2†	63.9	49.5
3	64.2	50.7

§ Serum measured after a run-in period on digitalis furosemide 80 mg and Slow K, 45 mEq daily. One patient received furosemide 40 mg and Slow K, 32 mEq daily. Serum measured after a run-in period on digitalis furosemide 80 mg and amiloride 10 mg daily.

values of 60 to 62 mEq/kg LBM found in normal subjects of both sexes.¹² The mean value of 51.6 mEq/kg LBM in trial patients was significantly lower (0.05 > P > 0.01).

Serum potassium and K₂O values were similar in the two groups and serum sodium was slightly higher in the trial group. The differences in serum uric acid did not achieve statistical significance and all other biochemical values were similar in the two groups.

Comparison of the effects of potassium supplements and amiloride in maintaining Ke in trial patients. Changes throughout the study periods are summarized in Tables III and IV and in Figs 1 and 2. No patient had overt evidence of fluid retention. Clinical status, weight and lean body mass were stable in all patients throughout the trial period. There was no significant change in Ke over the study period indicating that body stores of potassium were maintained adequately while on treatment with amiloride. There was a

Table IV Serial changes in trial patients

Patient No	Serum K (mEq/L)			K _e /LBW* (mEq/kg)			K _{RC} (mEq/L)			Serum uric acid (mg/100 ml)		
	Study period			Study period			Study period			Study period		
	1	2	3	1	2	3	1	2	3	1	2	3
1	3.6	3.7	4.0	40.6	43.0	55.3	94	97	102	8.6	11.7	8.4
2	3.4	3.5	3.6	50.6	46.7	50.8	99	99	100	8.6	15.6	8.6
3	3.4	3.7	4.1	45.9	58.0	44.5	97	100	94	9.0	9.4	7.1
4	3.9	3.7	4.1	59.1	60.8	42.0	100	93	97	12.0	10.8	8.9
5	4.7	4.4	4.3	53.2	50.6	56.4	101	107	105	10.7	17.9	9.3
6	3.9	4.0	4.0	59.2	53.4	47.5	93	96	94	10.3	8.5	7.1
7	—	3.6	3.9	—	46.9	46.3	—	93	97	—	7.6	9.4
8	4.2	4.3	5.9	47.0	60.6	43.4	90	105	91	7.9	10.7	7.1
9	4.2	3.5	4.2	53.0	45.1	49.0	96	102	97	11.7	14.0	8.0
10	4.1	3.8	3.6	51.8	37.2	32.3	97	105	92	6.7	8.6	6.1
11	3.6	3.5	4.4	55.9	53.5	58.2	100	96	95	10.3	9.3	6.4

*Total body Na

slight but significant rise in serum potassium following treatment with amiloride but no change in K_{RC}.

There was a significant fall in serum uric acid levels following treatment with amiloride. No changes were seen in blood urea, serum sodium, CO₂ content, creatinine, serum bilirubin, SGO1, alkaline phosphatase or one hour postprandial blood sugar.

The relationships between serum potassium and K_e and between K_{RC} and K_e are shown in Figs 3 and 4. Values for patients in both control and trial groups are included, but K_{RC} values were available in only three patients in the control group. No correlation was shown; the correlation coefficient for serum potassium/K_e was 0.17 and for K_{RC}/K_e was 0.24. Correlation was not improved by combining values for serum potassium and K_{RC} and comparing them with K_e by multiple regression.

Side effects. No side effects were reported by any of the patients who generally preferred amiloride to potassium supplements. However, one patient with severe multivalvular disease treated for 2 years with digitalis and diuretics died at the time of admission for final assessment (patient No. 9, Tables I and IV). Multiple ventricular ectopic beats had been present for five

months before the trial began and were not abolished by lowering digoxin dosage. Four months before the trial, the patient suddenly lost consciousness while watching television. The episode lasted about five minutes and may well have been due to a ventricular arrhythmia. Throughout the trial serum potassium and K_e values showed only random changes. During her final admission she developed ventricular fibrillation. Sinus rhythm was restored but idioventricular arrhythmias recurred and the patient died 24 hours later despite resuscitative measures. It was considered that death was related to severe underlying heart disease and it appeared unlikely that amiloride administration was a factor.

Discussion

In the past measurements of body potassium have been made either with the whole body counter or by calculating K_e. Sarveizer and Hughes³ considered the whole body counter more accurate, but in their study only single measurements of K_e were made, a procedure strongly criticised by Ikar and colleagues. These authors accepted that radioactive potassium was distributed among some 85 per cent of the body's potassium after 24 hours, which they considered the optimum period of

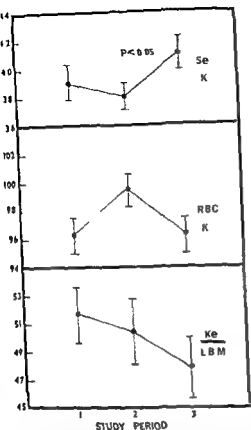
me 54
mb 1

Fig. 1 Changes in serum potassium (mEq/L) base (mEq/L) and Ke (mEq/kg LBM) in trial patients during the study periods. The only change to achieve statistical significance was the change in serum potassium between measurements 2 and 3. The change in Ke between measurements 1 and 3 was not significant. Bars show mean values \pm 1 S.D.

equilibration. Although the method is subject to the errors inherent in radioactive laboratory procedures, the accumulated evidence argues that results obtained are physiologically meaningful. Previous work indicates that the best assessment of body potassium is to consider the results obtained in relation to the subject's LBM as determined by measurement of IBW .⁸ Because body potassium and LBM fall proportionately in wasting disease, a reduction in Ke/kg LBM implies cellular loss of potassium.

Body potassium is reduced in patients with severe heart disease, especially when associated with heart failure,⁹ and with the use of potassium wasting diuretics.⁸ Some

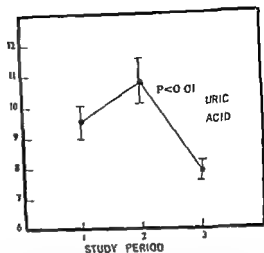


Fig. 2 Changes in blood uric acid (mg/100 ml) in trial patients during the study period. The changes between measurements 2 and 3 and between measurement 1 and 3 were both significant ($0.01 > P > 0.001$).

workers¹⁰ believe that the reduction of body potassium results from the wasting of lean body mass without additional cellular potassium depletion. Others have argued that cellular depletion of potassium is present^{11,12} predisposing to arrhythmias induced by digitalis or following heart surgery.¹³ Sometimes either conclusion can be drawn from the data.¹ For example, White and associates¹⁰ studied Ke in 42 patients with severe valvular heart disease, the majority of whom were on diuretics. Results were expressed in terms of predicted values for height based on the regression equation of Fleer and co-workers.⁸ Ke values were lower than predicted normal values but on the basis of additional data on body water and sodium it was concluded that the potassium deficiency was related to loss of cell mass rather than to cellular depletion of potassium. Figures of Ke/kg LBM calculated from White's data¹⁰ were 46 mEq/kg (males) and 47 mEq/kg (females) compared with normal values of 60 to 62 mEq/kg.^{8,7} This reduction in values of Ke/kg LBM implies cellular potassium depletion, contrary to the views expressed by the authors. Subsequently, White¹⁴ demonstrated a significant increase in exchangeable potassium following treatment with potassium supplements. In the present study, control and trial

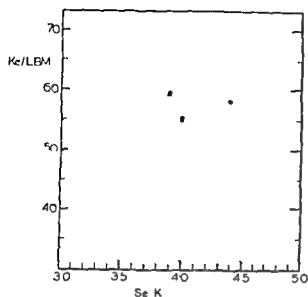


Fig 3 Relationship between serum potassium (mEq/L) and Ke/LBM (mEq/kg). Values are plotted for both control and trial patients.

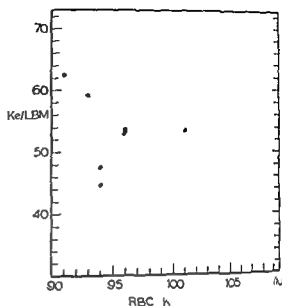


Fig 4 Relationship between RBC K (mEq/L) and Ke/LBM (mEq/kg).

groups were well matched except for the difference in sex distribution. Use of LBM allows for differences in the proportion of body fat in males and females and normal values for Ke/kg LBM are similar in both sexes.^{6,7} The variation in sex distribution should not therefore affect results.

All control patients had significant symptoms but were free of heart failure. As a group they did not show a reduction of Ke/Kg LBM although this observation does not deny the possibility that some patients may be so affected. By contrast trial patients on diuretics showed a reduction in Ke/Kg LBM despite full potassium supplements. It was concluded that cellular depletion of potassium was present in patients receiving diuretics but was not usually found in cardiac patients who were not receiving diuretics.

Values for TBW were higher than normal values reported in the literature suggesting that our patients may have shown an occult increase in extracellular fluid. This would appear unlikely however since lower values for TBW (and hence LBM) would give values for Ke/Kg LBM well above normal in control patients. Whatever the explanation for this observation differences in TBW do not appear responsible for differences in Ke/Kg LBM between control and trial patients, since average values for TBW/body weight in control

patients (61 per cent) were similar to those in trial patients (58 per cent). Differences between males and females are too small to affect these values significantly.

Amiloride in a dosage of 10 mg daily was free of side effects, the single death being considered unrelated. With two months therapy there was a small but significant rise in the mean value of serum potassium and a modest fall in Ke/Kg LBM which did not achieve statistical significance. This dose appeared approximately equivalent to 48 mEq of potassium chloride daily in maintaining body potassium but a higher dose would be required to increase Ke. The dose of 10 mg was chosen to avoid excessive diuretic action by the combined regimen in patients already free of heart failure. No harmful effects on renal or liver function or on blood glucose levels were demonstrated with amiloride therapy and there was no abnormal elevation of serum potassium.

High levels of serum uric acid in trial patients were presumably related to therapy with furosemide. Reduction of uric acid levels after the administration of amiloride is of considerable interest. In short term studies patients taking amiloride alone usually showed no change¹⁵ or a fall¹⁶ in serum uric acid with no change in uric acid clearance. In long term studies small groups of patients taking amiloride

in conjunction with thiazides or other proximally acting diuretics showed variable changes in serum uric acid some showing a rise some a fall¹⁷ and some no change¹⁸ Differences in therapy and in clinical status preclude firm conclusions from these studies

Furosemide induced hyperuricemia is poorly understood¹⁹ It may result from volume contraction from the induction of raised lactic acid levels which lead to the suppression of tubular secretion of uric acid or from a change in the intra/extracellular distribution of uric acid The majority of uricosuric agents are organic acids with the exception of zoxazolamine²⁰ Amiloride hydrochloride is the salt of a moderately strong base and it seems unlikely that it has a direct uricosuric effect in lowering uric acid levels in patients who are taking furosemide Further exploration of this effect on serum uric acid is indicated

As found in previous studies correlation between serum potassium and K_{RBC} was poor Certainly low values of serum potassium were always associated with low values of K_{RBC} but low values of K_{RBC} were frequently found with normal values of serum potassium Similarly correlation between K_{RBC} and K_{ECF} was poor This contrasts with conclusions of others who have suggested the K_{RBC} may be useful in predicting body stores of potassium²¹ No such prediction was possible over the range of values shown by our patients Correlation with K_{ECF} was not improved by taking into account both serum potassium and K_{RBC}

Summary

Patients with heart disease not requiring treatment with diuretics did not show depletion of body potassium expressed as K_{ECF}/kg LBM Patients treated with furosemide (80 mg daily) and potassium supplements (48 mEq daily) were depleted of potassium Treatment with 10 mg of amiloride daily was as effective as 48 mEq of potassium supplements in maintaining body potassium No side effects of the drug were noted but there was a significant reduction in serum uric acid after two months on the combined regimen of furosemide and amiloride No useful correlation was found between serum potassium or red cell potassium and K_{ECF}

Thanks are expressed to Dr R M L Whitlock for assistance with statistical procedures to Miss M Till for dietary surveys and to Mrs N M Hibbert and Miss H Nibbet for technical assistance Amiloride was kindly supplied by Merck Sharp and Dohme Ltd

REFERENCES

- 1 Singh B N Hurley P J and North J D K The use of amiloride in potassium depletion before cardiac surgery *Am HEART J* 78 22 1969
- 2 Flear C T G Cooke W T Sivyer A and Domenet J Measurement of total exchangeable potassium *Chim Chim Acta* 8 768 1963
- 3 Surveyer I and Hughes D Discrepancies between whole-body potassium content and exchangeable potassium *J Lab Clin Med* 71 464 1968
- 4 Moore F D Olesen K H McMurrey A H Parker H V Ball M R and Boyden C M The body cell mass and its supporting environment Philadelphia 1963 W B Saunders Company p 23
- 5 Singer M M Hoff R H Fisch M and DeGraff A C Red blood cell potassium—Therapeutic implications *JAMA* 187 14 1964
- 6 Talso P J Miller C E Carballo A J and Vasquez I K_{ECF} as a parameter of body composition *Metabolism* 9 456 1960
- 7 Moore F D Olesen K H McMurrey A B Parker H V Ball M R and Boyden C M The body cell mass and its supporting environment Philadelphia 1963 W B Saunders Company p 103
- 8 Olesen K H Body composition in heart disease Total exchangeable sodium total exchangeable chloride and derived values for body composition in cardiac disease with and without oedema *Acta Med Scand* 170 301 1964
- 9 Remenchuk A P Miller C Talso P J and Willoughby E O Depletion of body potassium by diuretics *Circulation* 33 796 1966
- 10 White R J Chamberlain D A Hamer J McAlister J and Hawkins L A Potassium depletion in severe heart disease *Br Med J* 2 606 1969
- 11 Schmitt G Hunt O R Lillenstein M and Brennan J C Sodium/potassium ratios in papillary muscle biopsies obtained during mitral valve replacement *J Thorac Cardiovasc Surg* 52 776 1966
- 12 Flear C T G Quinton A Carpenter R G Domenet J G and Sivyer A Exchangeable body potassium and sodium in patients in congestive heart failure *Clin Chim Acta* 13 1 1966
- 13 Lockett E Longmore D B Ross D N and Starnidge M F Potassium and open heart surgery *Lancet* 1 671 1966
- 14 White P J Effect of potassium supplements on the exchangeable potassium in chronic heart disease *Br Med J* 3 141 1970
- 15 Hitzberger G Kampfmeyer H and Conway J The diuretic effect of desmethyl

- pipazuronylguanidine (mk870) in man. *Clin Pharmacol Ther* 9:71, 1968
16. Peterson J W, Dollery C T, and Huston K M. Amiloride hydrochloride in hypertensive patients. *Br Med J* 1:422, 1968
17. Heffernan A G A. Serum enzymes and uric acid during treatment with Amiloride. *Lancet* 1:361, 1968
18. Voudoukis I J. Comparison of co-hydrodiuril and hydrodiuril in patients with hypertension. *Clin Res* 18:519, 1960
19. Steele I H, and Oppenheimer S. Factors affecting uric excretion following diuretic administration in man. *Am J Med* 4:564, 1969
20. Gutman A B. Uricosuric drugs. *Adv Pharm Sci* 4:91, 1966
21. Johns R V, Lawrence J I, O'Halloran M W, Wellby M I, and Worthley B W. Studies on total body serum and erythrocyte potassium in patients on maintenance haemodialysis. The value of erythrocyte potassium as a measure of body potassium. *Nephron* 7:30, 1960

A critical examination of the validity of the use of vein grafts in treating ischemic heart disease

Masayoshi Yokoyama MD
Tokyo Japan

Over the last thirty years numerous surgical procedures have been developed for the revascularization of the ischemic myocardium. At present aortocoronary artery bypass grafts are being used clinically to treat cases of ischemic heart disease.¹

This treatment is based on experimental studies with animals. In these studies sudden complete (acute) ligation of one of the major coronary arteries is followed by the anastomosis of a systemic artery and the peripheral coronary artery distal to the ligation. These cases demonstrate a significant blood flow directly to the coronary beds. The oxygenated bypassed blood protects the myocardium of the ligated coronary artery from acute ischemic changes.

These data have been used as a rationale to support the use of aortocoronary bypass grafts in numerous clinical cases.²⁻⁶ In most ischemic heart disease patients, however, coronary stenoses or occlusions develop much more slowly than in the experimental animal. Even if the coronary occlusion developed suddenly, the corrective operation is not undertaken in the acute stage rather, bypass grafts were usually inserted six or more months after the onset of acute occlusion.

To make the experiment more similar to

clinical cases, the left circumflex coronary artery of each dog was ligated. The dogs were then kept alive in this state for six months. After this period, the coronary artery distal to the ligation was then anastomosed to a systemic artery. The results of blood flow studies performed after this delayed operation differed greatly from those described in the literature in which the aortocoronary anastomosis occurred soon after the coronary ligation. In this paper, the authors carried out systemic to coronary anastomosis experimentally and measured the blood flow in the bypass grafts in both acute and chronic stages.

Materials and methods

Acute experiments Five mongrel dogs weighing 18 to 22 kilograms were anesthetized by the intravenous injection of sodium pentobarbital. Respiration was maintained through an endotracheal tube attached to a Bird respirator. The chest was opened through the left fourth intercostal space. The pericardium was incised anterior to the left phrenic nerve and the left circumflex coronary artery close to the origin was dissected free. The left subclavian artery was dissected from the aortic arch to its first branch and then transected. Aortic pressure was recorded through a catheter in

From the Heart Unit, 1st of Japan, Tokyo, Japan. Received for publication May 27, 1971.
Reprint requests: Dr. Masayoshi Yokoyama, MD, Heart Unit, 1st of Japan, Tokyo, Japan.
Address reprint requests to: Dr. T. K. J. 1st of Japan, 1st of Japan, Tokyo, Japan. Medical College 10

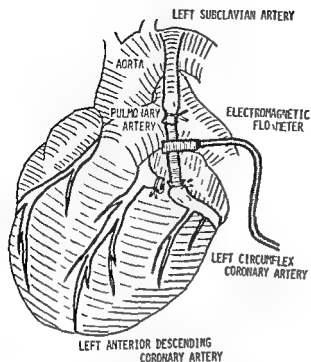


Fig 1 Schematic drawing showing the left subclavian artery anastomosed to the left circumflex coronary artery distal to the ligature. The electromagnetic flow probe is 2 mm in internal diameter. The bypass connecting tube is 7 cm in length.

serted retrogradely from the femoral artery. The tip of the catheter remained in the aortic arch. Pulmonary artery pressure was recorded by another catheter inserted directly into the main pulmonary trunk.

The circumflex coronary artery was ligated 1.0 cm from the bifurcation. A small catheter 0.2 mm in diameter was inserted into the distal end of the circumflex coronary artery, and the peripheral coronary artery pressure was measured. The pressures of the aorta, the pulmonary artery, and the peripheral circumflex artery were recorded simultaneously. As soon as the measurements of the distal coronary pressure were completed the bypass between the left subclavian artery and the peripheral coronary artery was established as shown in Fig 1. An electromagnetic flow probe 2.0 mm in diameter (MF 25 Nihon Kohden Kogyo Co., Ltd. Tokyo Japan) was placed in the bypass circuit. The total length of the bypass was 7 cm. Flow measurements were continued for two hours following the insertion of the bypass.

Chronic experiments In the chronic experimental series, the same anesthesia and thoracotomy procedures were used as in the

acute series. In five animals the left circumflex coronary artery was ligated 1.0 cm from the bifurcation.

The dogs were kept alive for six months. At this time they were anesthetized in preparation for surgery of the aortocoronary anastomosis. Prior to anastomosis of the left subclavian artery to the peripheral coronary artery distal to the ligature the peripheral circumflex coronary pressure was recorded with the simultaneous tracings of aortic pressure, pulmonary pressure, and electrocardiogram (ECG) of the second standard limb lead. In this chronic experimental series, a bypass circuit identical to the one used in the acute series was utilized (Fig 1). Flow measurements were recorded continuously for two hours following the establishment of the bypass.

Results

In the five cases of the acute experimental series, the peripheral coronary artery pressure distal to the ligature was 30 mm Hg—almost 25 per cent of the systemic blood pressure (Table I, Fig 2). Because of this marked pressure difference between the aorta and the peripheral circumflex coronary artery, the flowmeter in the bypass circuit recorded a significant blood flow to the coronary vascular beds (Fig 3). The aortocoronary bypass flow was remarkably high immediately following the insertion of the bypass because the myocardial ischemia induced during the pressure measurements reduced coronary vascular resistance distal to the anastomosis.

After the establishment of the aortocoronary anastomosis the ischemic myocardial area became hyperemic. This condition continued for approximately ten minutes. The aortocoronary flow gradually decreased to an average level of 38 ml per minute. Once the blood flow reached this level it remained constant for two hours.

In the chronic experimental series the peripheral coronary pressure increased markedly to a level approximately equal to the systemic blood pressure. The systolic pressure of the peripheral circumflex coronary was at least 55 mm Hg. The systolic pressure difference between the aorta and the peripheral circumflex coronary was approximately 10 mm Hg (Table II). Therefore the aortocoronary bypass graft

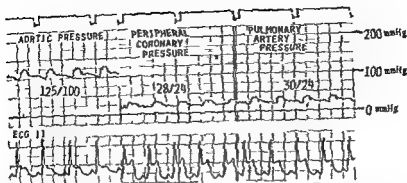


Fig. 2 Pressure recordings in Dog No. VG 27 immediately following the ligation of the circumflex coronary artery: the peripheral artery pressure is markedly low in comparison with the aortic pressure. ECG II shows the remarkable ST elevations.

Table I Data from acute experiments

Dog No.	Aortic pressure (mm Hg)	Peripheral circumflex coronary pressure (mm Hg)	Pulmonary artery pressure (mm Hg)	Systemic to-coronary flow (ml/min)
VG-22	110/83	30/20	30/22	35
VG-24	147/113	26/18	30/22	36
VG-25	160/134	34/28	22/15	40
VG-26	170/100	22/18	22/20	30
VG-27	125/100	28/24	30/24	50

Table II Data from chronic experiments

Dog No.	Aortic pressure (mm Hg)	Peripheral circumflex coronary pressure (mm Hg)	Pulmonary artery pressure (mm Hg)	Systemic to-coronary flow (ml/min)
VG-1	100/80	8/72	25/14	0
VG-1	120/100	110/95	28/20	3.0
VG-9	140/110	120/90	30/20	6.0
VG-11	108/90	98/83	25/15	10.0
VG-16	130/105	104/94	20/12	0

could not supply a significant amount of blood to the peripheral coronary beds in the chronic series (Fig. 4). Flowmeter recordings showed an average flow of only 4 ml per minute. The blood flow in the chronic series was significantly less than the aortic coronary flow in the acute experimental series.

Discussion

Many experimental reports concerning the systemic to-coronary anastomosis strongly support the efficacy of the bypass

graft. But these experiments were carried out under acute experimental conditions which did not consider changes in the peripheral coronary artery pressure after coronary stenosis. Although in acute cases the ligation of the major coronary artery initially induces low peripheral coronary pressure, the low peripheral pressure starts to increase slowly. The peripheral coronary pressures distal to the ligature can rise to the aortic pressure level. It may be controversial to correlate pressure directly with collateral flow; nevertheless many articles

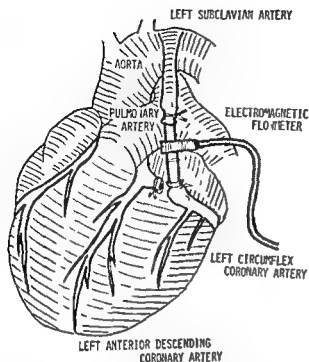


Fig 1 Schematic drawing showing the left subclavian artery anastomosed to the left circumflex coronary artery distal to the ligature. The electromagnetic flow probe is 2 mm in internal diameter. The bypass connecting tube is 7 cm in length.

sorted retrogradely from the femoral artery. The tip of the catheter remained in the aortic arch. Pulmonary artery pressure was recorded by another catheter inserted directly into the main pulmonary trunk.

The circumflex coronary artery was ligated 10 cm from the bifurcation. A small catheter 0.2 cm in diameter was inserted into the distal end of the circumflex coronary artery, and the peripheral coronary artery pressure was measured. The pressures of the aorta, the pulmonary artery and the peripheral circumflex artery were recorded simultaneously. As soon as the measurements of the distal coronary pressure were completed, the bypass between the left subclavian artery and the peripheral coronary artery was established as shown in Fig 1. An electromagnetic flow probe 2.0 mm in diameter (MF 25 Nihon Kohden Kogyo Co, Ltd 日本コフデン) was placed in the bypass circuit. The total length of the bypass was 7 cm. Flow measurements were continued for two hours following the insertion of the bypass.

Chronic experiments In the chronic experimental series the same anesthesia and thoracotomy procedures were used as in the

acute series. In five animals, the left circumflex coronary artery was ligated 10 cm from the bifurcation.

The dogs were kept alive for six months. At this time they were anesthetized in preparation for surgery of the aortocoronary anastomosis. Prior to anastomosis of the left subclavian artery to the peripheral coronary artery distal to the ligature, the peripheral circumflex coronary pressure was recorded with the simultaneous tracings of aortic pressure, pulmonary pressure and electrocardiogram (ECG) of the second standard limb lead. In this chronic experimental series a bypass circuit identical to the one used in the acute series was utilized (Fig 1). Flow measurements were recorded continuously for two hours following the establishment of the bypass.

Results

In the five cases of the acute experimental series, the peripheral coronary artery pressure distal to the ligature was 30 mm Hg—almost 25 per cent of the systemic blood pressure (Table I, Fig 2). Because of this marked pressure difference between the aorta and the peripheral circumflex coronary artery, the flowmeter in the bypass circuit recorded a significant blood flow to the coronary vascular beds (Fig 3). The aortocoronary bypass flow was remarkably high immediately following the insertion of the bypass because the myocardial ischemia induced during the pressure measurements reduced coronary vascular resistance distal to the anastomosis.

After the establishment of the aortocoronary anastomosis, the ischemic myocardium became hyperemic. This condition continued for approximately ten minutes. The aortocoronary flow gradually decreased to an average level of 38 ml per minute. Once the blood flow reached this level, it remained constant for two hours.

In the chronic experimental series, the peripheral coronary pressure increased markedly to a level approximately equal to the systemic blood pressure. The systolic pressure of the peripheral circumflex coronary was at least 85 mm Hg. The systolic pressure difference between the aorta and the peripheral circumflex coronary was approximately 10 mm Hg (Table II). Therefore, the aortocoronary bypass graft

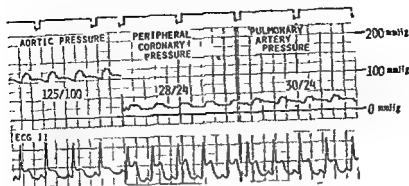


Fig. 2. Pressure recordings in Dog No. VG-77. Immediately following the ligation of the circumflex coronary artery, the peripheral artery pressure is markedly low in comparison with the aortic pressure. ECG II shows the characteristic ST elevations.

Table I. Data from acute experiments

Dog No.	Aortic pressure (mm Hg)	Peripheral circumflex coronary pressure (mm Hg)	Pulmonary artery pressure (mm Hg)	Systemic to-coronary flow (ml/min)
VG-27	110/85	30/20	30/21	35
VG-24	147/113	26/18	30/22	36
VG-25	160/134	34/28	27/15	40
VG-26	170/100	22/18	25/20	30
VG-27	175/100	28/24	30/24	50

Table II. Data from chronic experiments

Dog No.	Aortic pressure (mm Hg)	Peripheral circumflex coronary pressure (mm Hg)	Pulmonary artery pressure (mm Hg)	Systemic to-coronary flow (ml/min)
VG-1	100/80	85/77	25/14	0
VG-7	120/100	110/95	28/20	5.0
VG-1	140/110	120/90	30/20	6.0
VG-11	108/90	98/88	25/15	10.0
VG-16	130/105	104/94	20/12	11

could not supply a significant amount of blood to the peripheral coronary beds in the chronic series (Fig. 4). Flowmeter recordings showed an average flow of only 4 ml per minute. The blood flow in the chronic series was significantly less than the aortocoronary flow in the acute experimental series.

Discussion

Many experimental reports concerning the systemic to coronary anastomosis strongly support the efficacy of the bypass

graft. But these experiments were carried out under acute experimental conditions which did not consider changes in the peripheral coronary artery pressure after coronary stenosis. Although in acute cases the ligation of the major coronary artery initially induces low peripheral coronary pressure, the low peripheral pressure tends to increase slowly. The peripheral coronary pressure is still to the nature can rise to the aortic pressure level. It may be controversial to correlate pressure directly with collateral flow. Nevertheless, it is clear

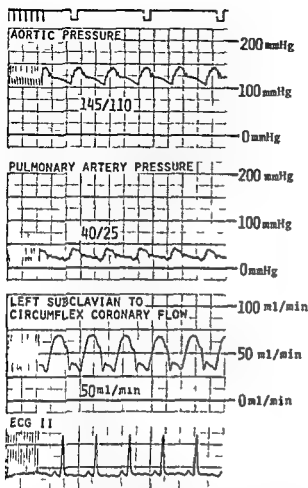


Fig 3 Systemic to-coronary flow studies in Dog No VC 27 (the same case as in Fig 2). The left subclavian artery has been anastomosed to the left circumflex coronary artery. The mean blood flow is 50 ml per minute. Elevated ST segments return to the base line after the establishment of the anastomosis.

clearly describe a significant increase of the peripheral coronary pressure. This increase is always demonstrated within a couple of weeks following the acute or chronic ligation of the coronary arteries.⁸⁻¹¹ Therefore in chronic cases a significant flow cannot be realized by the anastomosis of the peripheral coronary artery to the systemic artery. In our chronic experimental series the aortocoronary flow averaged only 4.0 ml per minute. This represents a maximum flow rate for these animals because no thrombosis, no stricture formation, and no histologic degeneration developed. Such developments might occur to some extent over a longer period of time; this would tend to decrease the initial flow rate of the anastomosed channel.

Postoperative angiographic studies may demonstrate that radiopaque materials travel from the aorta to the coronary artery through the venous bypass grafts in experimental as well as in clinical cases. Since the angiographic patency does not always indicate the presence of sufficient blood flow but only indicates anatomical continuity, the results of the angiographic studies do not serve as valid proof of physiologically functioning blood flow.

Judging from animal experiments venous bypass grafts can be very effective if they are performed immediately after sudden and complete occlusion of the coronary artery. In such cases the peripheral coronary pressure distal to the acute occlusion is still fairly low in comparison with the aortic blood pressure. However, the surgical treatment described in clinical reports differs considerably from that used in the animal experiments; in the former the time period between the occlusion and the operation was usually much longer.^{3,5}

The flow studies in clinical cases done by some reporters³⁻⁶ describe considerable flow right after the bypass procedure. Thus a significant discrepancy exists between our chronic experiment and these clinical reports. In the cases in which the coronary arteries are not totally occluded, surgical procedures of those arteries might have induced to some extent ischemic myocardial changes. If this is so, then the initial flow following the insertion of the bypass would be reasonably high because of the reduced myocardial vascular resistance. In these instances the constancy of the aortocoronary flow rate should be checked by observing it for at least 15 minutes after the operation.

Summary

Bypass grafts can carry blood from the aorta to the coronary arteries if the grafts are performed immediately following coronary occlusion. However, the grafts cannot carry any significant amount of blood if the coronary arteries have been occluded for a long period of time before the operation because the peripheral coronary artery pressure distal to the occlusion will already have increased to the aortic pressure level. Therefore, the use of venous bypass grafts

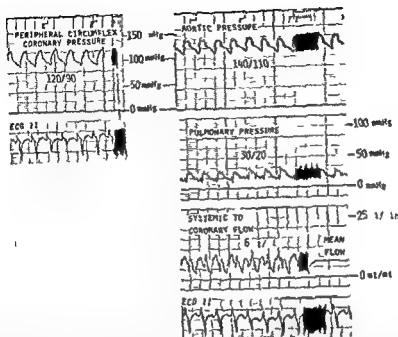


Fig 4 Pressure and flow recordings in Dog No 169 Six months after the ligation of the left circumflex coronary the peripheral coronary artery pressure is 120/90 mm Hg while the aortic pressure is 140/110 mm Hg The pressure difference between the aorta and the peripheral coronary is only 20 mm Hg Accordingly the anastomosis of the left subclavian artery to the peripheral coronary artery reveals the bypass blood flow to be only 6 ml per minute

should be restricted to those acute conditions in which the operation can be performed immediately following sudden coronary occlusions

The authors wish to express their appreciation to Mr Michael Reich for his editorial assistance

REFERENCES

- 1 Zimmerman H A And now—vein grafts *N Engl J Med* 285 1970
- 2 Reul G J Morris G C Jr Howell J F Crawford E S Wakasch D C and Sandford F M Coronary artery bypass in total obstructed major coronary arteries *Arch Surg* 107 313 1971
- 3 Morris G C Howell J F Crawford E S Reul G J Chapman D W Beazley H L Winters W L and Peterson P K The distal coronary bypass *Ann Surg* 172 652 1970
- 4 Mitchell B F Adam M Lambert C J Sungu U and Shiekh S Ascending aorta to coronary artery saphenous vein bypass grafts *J Thorac Cardiovasc Surg* 60 457 1970
- 5 Johnson W D and Lopley D An aggressive

- surgical approach to coronary disease *J Thorac Cardiovasc Surg* 59:128 1970
- 6 Favalaro R G Effler D B Groves L H Sheldon W C Shirey E K and Sones F M Severe segmental obstruction of the left main coronary artery and its divisions Surgical treatment by the saphenous vein graft technique *J Thorac Cardiovasc Surg* 60:469 1970
- 7 Yokoyama M Natural increase of the distal coronary pressure following acute ligation *Bull Heart Inst Japan* 35 1969
- 8 Elliot E C Jones E L Bloor C M Leon A S and Gregg D E Day to day changes in coronary hemodynamics secondary to construction of circumflex branch of left coronary artery in conscious dogs *Circ Res* 22 237 1968
- 9 Garamella J J George V P and Hay L J A correlative study of peripheral coronary pressure and coronary arteriography following coronary occlusion *Surg Gynec Obstet* 103 89 1957
- 10 Schaper W Jageneau A and Monneux R The development of collateral circulation in the pig and dog heart *Cardiology* 51:321 1967
- 11 Rees J R The myocardial collateral circulation *Br Heart J* 31:1 1969

Angina pectoris and slow flow velocity of dye in coronary arteries—A new angiographic finding

*A. I. Tambe, MD**

*M. A. Demany, MD**

*Henry A. Zimmerman, MD***

*J. Mascarenhas, MD****

Cleveland, Ohio

It has been classically stated that coronary arteriosclerosis, arterial hypertension and valvular heart disease form the basic etiologic substrates of all cases of angina pectoris.¹ Simply stated, anginal pain is a reflection of an ischemic myocardium. However, the routine use of selective coronary arteriography has partially uncovered the complexity of the anginal syndrome and we have become fully aware of the fact that typical angina may be present without angiographic evidence of coronary arteriosclerosis. Various theories have been postulated for the underlying mechanism, such as functional spasm, small vessel disease, abnormal oxygen, hemoglobin dissociation and myocardial cellular metabolic disturbances.^{2,3}

The purpose of this paper is to describe a new cinearteriographic feature, related to slow flow velocity of angiographic dye in 6 patients with the anginal syndrome and normal coronary arteries.

Materials and methods

Four of the 6 subjects were clinically presumed to have coronary artery disease in

light of a history of classical attacks of angina and electrocardiographic (ECG) changes, either at rest or after exercise. The two remaining subjects had atypical chest pain and epigastric pain. None had valvular heart disease, hypertension, pulmonary disease, thyrotoxicosis, collagen disorder, diabetes mellitus or anemia.

The laboratory investigations included blood count, fasting blood sugar, blood urea nitrogen, cholesterol, uric acid, calcium, phosphorus, serum proteins, serum enzymes, triglycerides, serologic tests, urinalysis, x-ray and fluoroscopic studies of the heart for size and configuration. Resting ECG, phonocardiogram and vectorcardiogram (VCG) were also completed. All 6 patients had an exercise tolerance test.

Right and left cardiac catheterization was carried out in the supine position and pressures were recorded with Statham strain gauge multichannel on an Electronics for Medicine recorder. Cardiac output was computed by the indicator dilution technique using the Lexington computer. Left ventricular function was assessed in terms of cardiac index, stroke

From the Marie L. Coakley Cardiovascular Laboratory, Saint Vincent Charity Hospital, Cleveland, Ohio.
Received for publication Aug. 27, 1971.

Reprint requests to Henry A. Zimmerman, M.D., 250 Hanna Building, Cleveland, Ohio 44115.

*Associate, Marie L. Coakley Cardiovascular Laboratory, Saint Vincent Charity Hospital, Cleveland, Ohio.

**Director, Marie L. Coakley Cardiovascular Laboratory, Saint Vincent Charity Hospital, Cleveland, Ohio.

***Fellow, Marie L. Coakley Cardiovascular Laboratory, Saint Vincent Charity Hospital, Cleveland, Ohio.

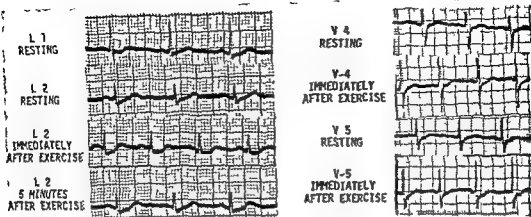


Fig 1 Positive exercise tolerance test in 7 patients with normal selective coronary artery rights who displayed slow di flow

Table 1 Physical and hemodynamic values in six patients with anginal syndrome and normal coronary arteries

Case no	Heart rate (beats per min)	Aortic pressure (mm Hg)	Right main values (mm Hg)	Cardiac index (L/min ²)	Stroke index cc/beat/M ²	Left EDPI (resting) (mm Hg)	Left EDPI (exercise) (mm Hg)	Aortic flow (l/min)
1	54-60	75-80 to 100/60	5	2.1	38.3	17	15	94
2	83	90/70	4	3.8	37	5	rate 140 no exercise	96
3	50	130/70	5	2.7	38	15	15	94
4	67	130/70	3	4.3	49	7	17	95
5	71	90/60	6	3.5	49	7	8	95
6	110	100/75	5	3.8	34	8	8	93

R.L. = Right (mm Hg)
L.L. = Left (mm Hg) and diastolic pressure

index and left ventricular end diastolic pressure recorded at rest and following supine leg exercise for three minutes. Left ventriculography was performed in the right anterior oblique position and the left ventricle was evaluated by inspection for cavity size disorders of contractility and the presence of mitral regurgitation. Selective coronary arteriography was carried out using meglumine diatrizoate (Renografin 60). Cinearteriography was recorded at 60 frames per second in the right anterior oblique, left anterior oblique and posterior anterior projections before and after the administration of sublingual Isordil. The venous phase following coronary artery opacification was recorded in cinearteriogram in two instances.

Results

All 6 patients had abnormal resting ECGs. Two patients had evidence of septal fibrosis on their resting tracings manifested by poor progression of the R wave from V₁ through V₂. One subject had diffuse ischemic changes and QS complexes in Leads III and aV_F suggestive of an inferior myocardial infarction. The remaining 3 subjects had diffuse ST and T wave changes compatible with myocardial ischemia. Three patients out of the 6 had a positive exercise tolerance test (Fig 1). Cardiovascular hemodynamic data are summarized in Table 1. All 6 subjects had normal right atrial pressures. The cardiac index was slightly decreased in Cases 1 and 3 and was normal in the others. Case 3 had



Fig 2 A B and C Right coronary arteriograms A frame 1 B frame 7 C frame 8 Note the strikingly slow flow velocity of dye between frame 1 and frame 8

a slightly elevated resting left ventricular end diastolic pressure (normal 12) which did not change following supine leg exercise. Cases 1 and 4 displayed mild and moderate rise following leg exercise, respectively.

The left ventriculogram in Cases 2 and 3 displayed moderate dilatation and dyskinesia. In Case 5 the left ventricle was of normal size, however myocardial contractility appeared to be somewhat impaired. The left ventricular angiogram was normal in the other subjects.

Coronary arteriograms

Optimal quality in selective coronary arteriography was obtained. The coronary arterial tree was of normal caliber in all 6 subjects. There were no luminal irregularities throughout the major and secondary branches. However the flow of dye in the visualized vessels featured a strikingly slow flow velocity resulting in marked delay in the clearance of the contrast medium from the coronary arterial tree (Figs 2, 3, 4 and 5). The use of sublingual Isosorbide Dinitrate did not affect the caliber of the vessels or the velocity of flow. The slow flow velocity was consistently reproducible in different projections and was not altered by repositioning the tip of the catheter. Monitoring of cardiac rate and central aortic pressure during coronary arteriography did not reveal any significant decrease in heart rate, fall in arterial pressure, or increased duration of systolic myocardial contraction. These are important considerations since an alteration in any of these factors could lead to a decrease in the velocity of flow along the coronary arterial tree.

Discussion

Perfusion deficit of the myocardium regardless of the cause remains the underlying mechanism of the anginal syndrome. The regulation of coronary blood flow is under the influence of several physiological factors which can be schematically divided into remote versus local factors.

Remote regulation of coronary blood flow. Both alpha and beta receptors are present in the small vessels of the myocardium. In the presence of an ischemic myocardium there is an overall beta stimulation and vasodilatation. Cholinergic stimulation also seems to induce coronary vasodilatation. Coronary blood flow is intimately related to the available oxygen per liter of blood flow. Arterial hypoxemia increases coronary blood flow, tending to keep tissue P_{O_2} constant. The pH on the other hand exerts some effect on the hemoglobin oxygen dissociation curve, an acid pH leading to a shift of the curve to the right.

Local factors. Myocardial perfusion is a direct function of the pressure head at the coronary ostium and is an inverse function of the arteriolar and capillary resistance.¹ However, due to the fact that coronary circulation occurs mainly in diastole, the diastolic phase of the cardiac cycle and the diastolic component of the blood pressure play a primary role in coronary circulation. In our present series the central aortic diastolic pressure was adequate in all subjects and could not account for the slow flow velocity during selective coronary arteriography.

Myocardial tissue pressure—i.e. the extravascular component of coronary resistance increases from epicardium to endo-



Fig 3 A and B Coronary arteriograms. A frame 1. Right coronary artery smooth vessel. B frame 10. Segmental holdup of dye at mid level and terminally.

cardium exceeding intermittently the intraventricular pressure⁶ and leading to a nonhomogenous myocardial perfusion. Carson and Lazzara⁶ noted a decrease in myocardial contractility resulting in a marked increase in coronary blood flow during coronary arteriography in dogs which leads us to speculate that the slow flow velocity of dye noted in our subjects was not the result of the direct intracoronary injection of the contrast medium.

Intravascular resistance

Coronary arteriosclerosis remains the major cause of the anginal syndrome. The mechanically obstructed coronary artery fails in the absence of collaterals to deliver adequate blood supply distally thus resulting in myocardial perfusion deficit and angina. Granted that selective coronary arteriography tends to underestimate luminal irregularities it is highly unlikely with our present technique⁸ that significant luminal disease would be missed when interpreting the cinearteriographic results. In our present study all coronary vessels down to a caliber of 1 mm were interpreted as normal by two observers.

Another important cause of transient coronary luminal narrowing and slow flow of dye is a functional spasm of the coronary artery under study.⁹ Typical anginal attacks that have been precipitated during selective coronary arteriography by a marked and localized coronary artery spasm have responded dramatically to coronary vasodilators. In our present



Fig 4 Coronary arteriogram. Residual dye coating the conus branch and the terminal right main trunk.

study no functional spasm was demonstrated at any time during the procedure that would account for the slow flow velocity of the dye. Nevertheless all patients were given sublingual coronary vasodilators to see if the velocity of flow would be significantly affected. Small vessel resistance remains the most important and yet the most controversial factor involved in regulating regional myocardial perfusion. Small variations in the luminal diameter of these vessels lead to profound alterations in myocardial blood flow.

There is little doubt that small vessel pathology is quite common in such disorders as collagen diseases, amyloidosis, idiopathic myocardopathies, diabetes mellitus, certain hypersensitivity states and hematologic disorders. However we are still in the speculative stage when dealing with small

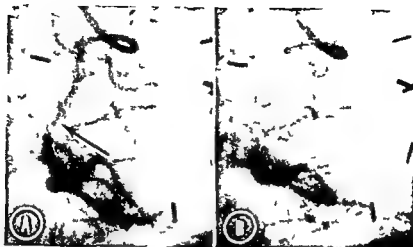


Fig. 5 A and B Coronary arteriograms. A frame 1. Right coronary artery with severe segmental obstructive disease. B frame 10. Note the rapid clearance of dye through the obstructed segment.

vessel pathology in arteriosclerotic heart disease^{10,11} and in the anginal syndrome with grossly normal coronary arteries.

It is universally accepted that an imbalance between oxygen supply and demand leads to the myocardial hypoxia which is the underlying pathology for angina pectoris. In our 6 subjects there was no cine arteriographic evidence of coronary arteriosclerosis. On the other hand physical and hemodynamic findings did not reveal any significant disturbances in the oxygen carrying capacity of blood such as anemia, chronic obstructive lung disease, or cardiac decompensation with peripheral venous hypertension and stasis.

In the present study we are therefore led to assume that the slow velocity of dye noted during selective coronary arteriography was somehow related to an abnormal increase in small vessel resistance resulting in restricted oxygen delivery. Physiochemical alterations in situ or localized hypersensitivity reaction brought about by the direct contact of dye with the intima remain a possibility.

A decrease in the number of perforators and in straight and narrowed major coronary vessels have been observed in angiograms of patients with obscure myocardial pathologies.¹² Disorderly medial proliferation of small vessels and lesions similar to medial necrosis have been found in one of these patients. It was suggested that perhaps the arteriolar histologic alterations precede those of the myocardium. Although a similarity in arteriographic findings is

lacking the same conclusions may perhaps apply to our 6 subjects. 2 of whom displayed dilated and hypocontractile left ventricles on their angiograms. These findings may reflect the early changes of myocardial dysfunction seen in cardiomyopathies. Needless to say myocardial biopsy would have been of the utmost importance in defining the histologic structure of the myocardium.

Summary

The coronary arteriograms of 6 patients with the anginal syndrome revealed a normal coronary arterial tree. This finding was associated with a strikingly slow flow rate of the angiographic dye through the major vessels. This feature is discussed in detail and a theory of small vessel disease is suggested. The purpose of this paper is to bring into focus a new angiographic finding. Its cause is hypothesized and requires clarification by further studies which should include accurate flow measurements, metabolic determinations, and myocardial biopsies.

REFERENCES

- 1 Zoll P W, Weisler S, and Blumenthal H J. Angina pectoris: A clinical and pathologic correlation. *Am J Med* 11:331, 1951.
- 2 Kemp H C, Elliott W C, and Corbin R D. The anginal syndrome with normal coronary arteriography. *Ann Assoc Am Physicians* 80:59, 1967.
- 3 Neill W A, Kischbaum D C, and Judkins M P. Myocardial hypoxia is the basis for angina pectoris in a patient with normal

- coronary arteriograms N Engl J Med 279 789 1968
- 4 Cross C E Rieben P A and Stribury P F Coronary driving pressure and vasomotor tonus as determinants of coronary blood flow Circ Res 9 589 1961
- 5 Kirk E S and Hong C R Nonuniform distribution of blood flow and gradients of oxygen tension within the heart Am J Physiol 206 661 1964
- 6 Carson J P and Lazzara R Hemodynamic responses initiated by coronary stretch receptors with special reference to coronary arteriography Am J Cardiol 24 571 1970
- 7 Lakoff W Segal B L and Karpman H Paradox of normal selective coronary arteriogram in patients considered to have unobstructable coronary heart disease N Engl J Med 266 1063 1967
- 8 McLaughlin W Demany M A Tambe A V and Zimmerman H V Coronary arteriography Devices for the improvement of the cineradiographic system Am J Cardiol 21 549 1968
- 9 Demany M V Tambe A V and Zimmerman H V Coronary arterial spasm Chest 53 714 1968
- 10 Saphir O Ohniger I and Wong R Changes in the intramural coronary branches and coronary arteriosclerosis A M A Arch Pathol 62 159 1956
- 11 More B M and Simmons S C The status of the myocardial arteries in angina pectoris Am Heart J 61:123 1961
- 12 Vasmataz L Hemrick B Paulin S and Ryden B Obstructive cardiomyopathies with coronary arteriographic changes Am J Cardiol 19 531 1967

The relation between the conductivity of the blood and the body tissue and the amplitude of the QRS during heart filling and pericardial compression in the cat

Mordechai Manoach M Sc Lng *
Simon Gitter Ph D M D
Edith Grosman M Sc
Daliah Varon B Sc
Tel Aviv Israel

The QRS amplitude in poikilotherms¹ and in homeotherms² changes during bleeding or filling of the heart. Studies dealing with the significance of the amplitude changes of the QRS began in 1910.¹ The changes were confined to the conductivity of the fluid inside^{3,4} and outside⁵ the heart and of the immediate surrounding tissues.^{6,10}

In a previous investigation¹¹ it was shown that the decreased amplitude of the QRS waves during filling of the turtle heart is not connected with changes of the short circuit inside the heart caused by the blood.

The aim of this work is to examine if the changes of the QRS in mammals occurring during changes in filling of the heart are a function of conductivity inside and outside the heart. Changes in heart filling can be achieved in experimental animals by direct and indirect means. (1) In a direct way by taking out blood from the circulation⁴ or pumping in an extra amount of liquids

(2) in an indirect way by compression of the heart with the help of liquids introduced into the pericardial sac. This compression reduces the heart filling. The influence of short circuits caused by the conductivity of the blood on the QRS amplitude can be examined by filling the heart or the pericardial sac with solutions of known but different conductivity. The solutions used in our experiments were: saline—isotonic NaCl solution with a conductivity similar to that of blood and body tissue; isotonic glucose solution 5 per cent and olive oil both of a very low conductivity.

Methods

The experiments were carried out in adult male and female cats. Anesthesia was induced by 30 mg. per kilogram of body weight of intraperitoneal sodium thiopentone. Cannulas were introduced into the trachea, femoral artery and femoral vein

From the Department of Physiology and Histology, Tel Aviv University, Tel Aviv, Israel.
Received for publication Aug. 30, 1971.
Reprint requests to Prof. M. Manoach, Department of Physiology, Tel Aviv University, Ramat Aviv, Tel Aviv 6100.
*This work is a part of a Ph.D. thesis to be submitted to Tel Aviv University Medical School.

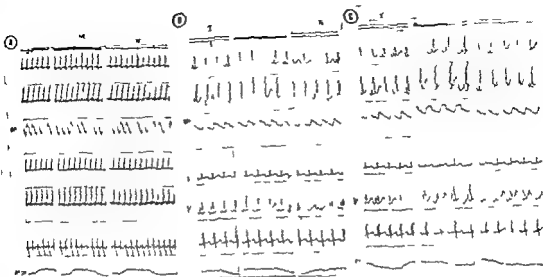


Fig. 1 ECG recording from cat before intraventricular filling (I) during the filling (II) and after return to the normal (III) with saline oil and glucose. Lead I II III V₁ V₂ V₃ V₄ V₅ V₆ and Z are shown. BP = Blood pressure. Resp = Respiration.

Heart catheters (gauge 10) were introduced into the left ventricle through the carotid artery for the purpose of additional filling of the ventricle with 1 to 10 ml of either isotonic saline isotonic glucose solution or olive oil. Overfilling of the heart during normal circulation was achieved by injection of one of these fluids into the left ventricle at the rate of 0.5 to 1 ml per second. With each systole an increased volume (blood plus injected solution) was thrown out into the circulation. At the cessation of the injection the overfilling was stopped and heart filling thereby returned to normal. The state of overfilling therefore existed during the period of intraventricular injection of liquid. Recordings of the ECG were obtained before the overfilling during the overfilling and after the cessation of the overfilling.

In some animals the injected olive oil produced immediate coronary artery emboli already present during overfilling. It was possible however to carry out experiments in which no heart emboli occurred and the electrocardiogram continued to be normal for prolonged periods. The results taken into account refer to those experiments only in which the ECGs before and after overfilling were similar.

The experiments with pericardial compression were carried out in cats artificially

respirated by a Howard Respiratory pump (model 670). The rib cage was cut next to the sternum and aspirated with a retractor. The intact pericardium was fixed to the side of the open chest by silk sutures and a cannula was introduced into the pericardial sac for the purpose of filling. At the end of the experiment the fluid was removed from the pericardial sac through the same cannula. Control experiments were carried out in cats under the same conditions but with open pericardium. The upper side of the fixed pericardium was cut. The heart was lying in the open pericardial sac as in a bath. The intact pericardium as well as the open one was filled with either saline or olive oil.

Standard ECG Leads I II III C₁, and CR₂, as well as the scalar tracings V₁, V₂ and Z were recorded in all experiments using a Grass model 7 six channel polygraph.

Results

Fig. 1 shows the changes in QRS amplitude recorded in cats before overfilling of the heart (part I) during the overfilling (part II) and after return to normal (part III). The figure clearly shows that the QRS amplitude increases in all the filling experiments regardless whether saline solution glucose or olive oil were used. The increase

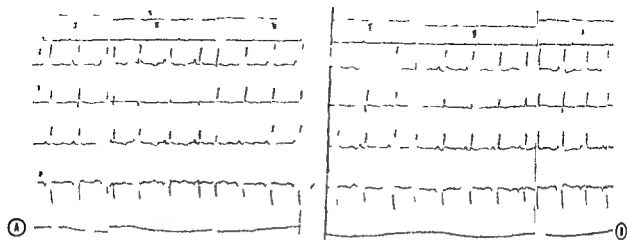


Fig. 2 ECG recording from cat before the filling of the pericardial sac (I) during the filling (II) with saline or oil and after the removal of the fluid (III). Abbreviations as in Fig. 1.

was recorded in all the standard leads as well as in the scalar tracings X, Y, and Z.

Fig. 2 shows the changes in the QRS amplitude recorded before filling of the pericardial sac (part I) during filling (part II) and after removal of the fluid (part III). Filling of the pericardial sac produced compression of the heart reduced filling increased venous pressure and decreased arterial pressure. In Fig. 2 it was clearly shown that even under compression with olive oil the amplitude of the QRS complex changes as in the case with saline. In both cases the amplitude of QRS was reduced during compression of the heart (part II) and returned to its original amplitude when the fluid was removed (part III).

In the control experiments (Fig. 3) when the open pericardial sac was filled with saline or with olive oil compression on the heart did not occur. In these experiments there were no significant changes in the QRS amplitude during filling with saline and no changes at all with olive oil when compared with the amplitude before filling.

Discussion

The turtle heart reacts to bleeding with an increase of the QRS amplitude⁶ while refilling immediately produces the reverse effect.¹ According to Krasno and associates⁶ influence of bleeding can be explained by the reduction of shunting circuits inside the empty heart. The mammalian heart reacts to bleeding with a decrease of the QRS

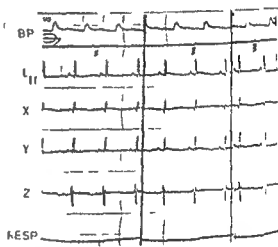


Fig. 3 ECG recording from cat before the filling of the open pericardial sac (I) during the filling with saline (II) or with oil (III).

amplitude.⁴ A phenomenon reversed by refilling the heart with blood or saline. Overfilling causes an increase of the QRS amplitude.⁴ These reactions have also been ascribed to the changes in the conductivity of intracardiac blood.³

If the effect of bleeding on the QRS amplitude were dependent only on the conductivity of the intracardiac fluid one would expect the turtle and the cat to react in an identical way to bleeding and not in an opposite manner as in this case. The experimental evidences brought in the previous¹¹ and present work show that the different specific conductivity of substances used had no influence on the changes of the QRS amplitude during overfilling—all of them (saline and glucose solution as well as olive oil) produced the same reaction.

Ishikawa and co workers¹ showed that during heart failure the QRS amplitude is decreased although the heart size is increased. They showed that following clinical improvements the QRS amplitude increased accompanied by decrease in cardiac volume. The fact that overfilling of healthy heart in cats (with either blood, saline, glucose or olive oil) causes the same increasing in the QRS amplitude as is observed during clinical improvement of heart failure shows that the short circuit effect of the increased intracavity blood mass² cannot explain the changes in the QRS amplitude we are dealing with. Therefore conductivity cannot be the main cause.

In our previous investigations^{1,11,12} the alterations of the QRS amplitude caused by bleeding were related to the changes in the filling of the normal heart i.e. changes in stretching of the heart and not heart size itself which have different meanings in the healthy heart or in heart failure.

The dissimilarities between the reactions in turtles and cats are related to phylogenetic differences¹³.

In pericarditis where the pericardial sac is filled with good conducting fluids the reduction of QRS amplitude is known. This phenomenon has been explained by the short circuits outside the heart.⁹ The evidence in this work proves that conductivity of infused fluids (either saline or olive oil) has no influence on the decrease in the QRS amplitude. Moreover the fact that filling the open pericardial sac with olive oil did not change the QRS amplitude while filling the intact pericardial sac did underlines the independence of this phenomenon on the conductivity. The changes in QRS amplitude caused in pericardial effusion therefore may also be explained by the decreased heart filling caused by the cardiac compression.

With regard to the initial question whether a relation exists between the conductivity of blood and body tissue and the QRS amplitude we conclude that the conductivity of the fluids inside and

outside the heart has no influence on the alteration of QRS during bleeding, pericardial effusion and overfilling of the ventricle. They originate from the changes in the state of filling of the normal heart—stretching the healthy heart.

REFERENCES

1. Staal H. Zur Analyse des Elektrokardiogramms nach Versuchen am isolierten Froschherzen. *Z Biol* 53:49 1910.
2. Lepeschkin E. Modern electrocardiography. Baltimore 1951. The Williams and Wilkins Company. p. 451.
3. Angelikos E T and Gekkin A. Influence of venous inflow volume in the magnitude of the QRS potential in vivo. *Cardiol* 12:337 1963.
4. Manoach M, Gitter S, Grossman E, Varon D and Gasser S. The influence of hemorrhage on the QRS complex of the electrocardiogram. *Am Heart J* 82:55 1971.
5. Manoach M, Varon D, Grossman E, Gitter S and Sroka M. Influence of bleeding on the QRS amplitude in adult chickens and chick embryos. *Br J Med Sci* 1:108 1971.
6. Krasno M R, Eyster J A F and Van Le C A. The nature of the T wave potential in the tortoise heart. *Am J Physiol* 114:119 1933.
7. Brody D A. A theoretical analysis of intracavity blood mass influence on the heart lead relation. *Circulation* 41:731 1956.
8. Nelson C A, Chatterjee M, Angelikos E T and Hech H H. Model studies on the effect of the intracardiac blood on the electrocardiogram. *Am Heart J* 62:83 1961.
9. Wilson F N, Wishart S W and Herrmann C R. Factors influencing distribution of potential differences produced by heart beat at surface of body. *Proc Soc Exp Biol Med* 23:276 1926.
10. Eyster J A F, Marsh F and Krasno M R. The nature of the electrical field around the heart. *Am J Physiol* 106:574 1933.
11. Manoach M, Grossman E, Varon D and Gitter S. The relation between the conductivity of the blood and the body tissue and the amplitude of the QRS in heart filling and pericardial compression. *Proc Seventh Natl Conf I E F E Israel* 1971 p. 810.
12. Ishikawa K, Berson A S and Lipberger H A. Electrocardiographic changes due to cardiac enlargement. *Am Heart J* 81:35 1971.
13. Manoach M and Gitter S. QRS amplitude response to bleeding in adult hemothorax and pericarditis and during fetal development. In press.

Interrupted eccentric longitudinal muscle fibers of the kidney and adrenal veins

Hushang M Pavan MD

Ind J Gilbert MD

Ishpeming Mich

The walls of the small veins, in general like those of the corresponding arteries consist of three tunics. The intima is composed of the endothelium and a poorly defined internal elastic membrane. The adventitia is usually the thickest coat and it is formed by collagenic connective tissue. The media is much thinner than that of the companion artery and it consists chiefly of circularly arranged smooth muscle fibers. In some veins the inner muscle fibers of the media have a longitudinal course. The veins of certain organs such as the maternal placenta and bed retina, bone brain and meninges are devoid of muscle fibers. In contrast veins of the pregnant uterus umbilical cord and adrenal glands are rich in muscle fibers. In the adrenal glands of man, both the main and medullary veins show a weak development of circular muscle and extremely thick longitudinal musculature.¹

In 1906 Purkerson noted that large longitudinal ridges of smooth muscle in the walls of the veins of the adrenal glands are constantly present in human subjects less highly developed in the suprarenal vessels of the lower mammals and may to some extent serve the purpose of the valves

In 1925 Goldzieher and Sherman² pointed out the association of hypertrophy of the longitudinal musculature of the suprarenal veins and hypertension. In 1937 Franklin³ described the presence of a thin circular and an extremely thick longitudinal muscle layer in the walls of the veins of the adrenal glands of adult man. He also indicated that the adrenal veins of the ox and other mammals do not show such a muscular development. In 1944 Goldzieher² pointed out that the adrenal veins are characterized by a singular feature the unique development of longitudinal muscle bundles in the wall of the larger veins. He also postulated that muscle bundles act as regulators not only of the venous flow but also of the adrenal secretion. Symington⁴ in 1962 contended that muscle bundles of the adrenal veins are concentric in the midportion of the gland but change into eccentric bundles at the periphery. Contraction of the eccentric muscle bundles will obstruct the blood flow from the cortical capillaries into the central vein without interfering with the blood flow in the main vein. The longitudinal muscle in the central vein accordingly has a valvular action and controls the flow of the blood from the adrenal

Is in the Departments of Pathology at University of Wisconsin School of Medicine Milwaukee Wis Clarkshre Veterans Administration Hospital Waukesha Wis University of Chicago W Va a 11 n A Bell Memorial Hospital Ispeming Mich

Received for publication Aug 30 1971

Reprint request to Hushang M Pavan MD Department of Pathology Bell Memorial Hospital Ispeming Mich 49849

Table 1 Interrupted eccentric longitudinal muscle fibers of human kidney and adrenal veins

Groups	Age		Kidney			Adrenal		
	Average	Range	FM/No sections	F	M	FM/No sections	F	M
1 Newborn	10 days	1-60 days	0/170	0 o	—	0/187	0 c	—
2 Infant	8 mo	2-24 mo	0/160	0 o	—	0/156	0	—
3 Children	6 yr	2-15 yr	8/167	5 o	2+	24/96	23	2+
4 Young adult	23 yr	16-30 yr	88/265	33 c	3+	84/140	43 o	3+
5 Middle age	38 yr	31-45 yr	50/704	25 c	3+	96/140	15	3+
6 Middle age	53 yr	46-60 yr	31/150	20 c	3+	107/134	75 o	3+
7 Aged	69 yr	61-91 yr	97/230	40 o	3+	87/110	10	3+

F = fibrous
M = muscular
o = occasional
c = common

Table II Interrupted eccentric longitudinal muscle fibers of rat kidney and adrenal veins

Group (No)	Body weight		Daily treatment DHT	Kidneys			Adrenals		
	Initial	Final		No sections	F	M	No sections	F	M
1 (12)	50	65	—	90	1+	0	160	0	0
2 (10)	150	165	—	170	1+	0	60	0	0
3 (17)	380	380	—	80	1+	0	120	0	0
4 (10)	210	190	1 wk	75	1+	0	81	0	0
5 (10)	210	200	2 wk	75	1+	0	80	0	0
6 (10)	210	200	3 wk	60	1+	0	40	0	0
7 (10)	220	180	4 wk	75	1+	0	58	0	0

D = male DHT = daily treatment F = fibrous M = muscular
Retired breed rats

cortex. In 1967 Pavan and Gilbert⁷ described the hypertrophy and fibrosis of the longitudinal muscle fibers as micronodular phibosclerosis suggesting an association with age and stress. Such nodules were also found in the wall of the small veins of the kidneys.

The aim of the present study was to determine the age at which these muscle fibers are noted first in human subjects; the frequency of the fibrous and muscular fibers in various age groups; the amount of muscle versus fibrous tissue; the morphology of the fibers; and finally the presence or absence of the fibers in the sections of the adrenal glands and kidneys of rats.

Materials and methods

An arbitrary age group arrangement was made as follows: newborn 1 to 60 days; infants 2 to 24 months; children 2 to 15

years; young adults 16 to 30 years; mature adults 31 to 45 years; middle age 46 to 60 years; and aged 61 years and over. Among the autopsies of several years 10 consecutive cases were picked out for each age group with fresh tissue of the kidneys and adrenals available. Multiple sections were prepared with an attempt to examine all parts of the organs including the hilum and the periphery. Half of the sections were stained by hematoxylin and eosin and the other half by Gomori's trichrome method to differentiate between fibrous tissue and muscle fibers. Presence or absence of the fibrous or muscle bundles was graded as absent (0), minimal (1+), moderate (2+), and large amount (3+). An average was calculated for each group as indicated in Table I. The number of the sections prepared of human kidneys and adrenals was 2,319. History, physical findings, blood

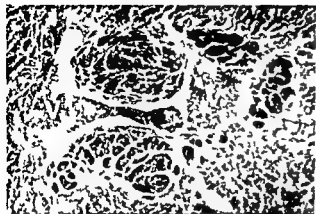


Fig. 1 Interrupted eccentric longitudinal muscle fiber are noted in the wall of a vein (1) in the central part of the adrenal gland. Severe hypertrophy of a muscle bundle is seen in the upper part of the photograph causing partial occlusion of the lumen of the vein (Gomori's trichrome X40)

pressure, diagnosis and autopsy findings were noted in each case.

In the animal experimentation part of the study 74 female Sprague Dawley rats of various weights were divided into 12 groups as indicated in Table II. The animals were subdivided into groups of 3 to 5. They were kept in suspended metal cages and had free access to water and Purina Laboratory Chow. The animal quarters were air conditioned and the temperature was kept around 75° F at all times. Some of the groups were treated by dihydrotrichysterol (DHT) at the dose of 50 µg in 0.5 cc of corn oil given by mouth daily.⁸ This was done to produce progeria-like syndrome and severe arteriosclerosis in a short period of time.⁹ The length of the DHT treatment varied among the groups from 1 to 4 weeks as indicated in Table II. At the end of the experiments, all animals were put to death by ether. The kidneys and adrenals were removed and fixed in Bouin's solution for 48 hours after which they were sectioned and processed for microscopic examination. The total number of slides prepared from rat kidneys and adrenals was 1173. Half of the slides were stained by hematoxylin and eosin. The rest by the trichrome technique for observation of the muscle fibers.

Results

The longitudinal muscle fibers along the course of the small veins were found not only in the adrenals but also in the human

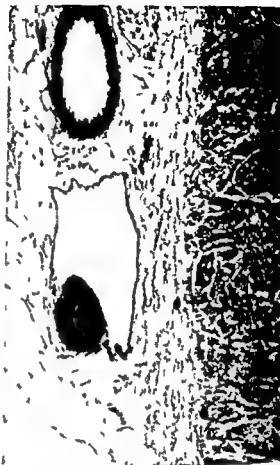


Fig. 2 Eccentric muscle bundles are noted in the wall of a small vein outside and adjacent to the adrenal gland (Trichrome stain X40)

kidney sections. A large amount of fibrous tissue is noted surrounding the neurovascular complex entering the hilum of the kidney. This is true both for human as well as rat kidneys. Longitudinal muscle fibers however are completely absent in the sections of the kidneys and adrenals of the rats. The connective tissue present at the hilum of the kidneys extends into the parenchyma along with the blood vessels. Longitudinal muscle fibers are noted in the wall of the veins in the hilum of the kidneys as well as in the parenchyma. The amount and the frequency of their presence however reduce as the neurovascular complex travels deeper into the parenchyma. They are seen occasionally in the subcapsular region of the kidneys. Occasionally veins outside of the adrenal in the adipose tissue surrounding the gland were found demonstrating the eccentric longitudinal muscle fibers.

Several adrenal glands not indicated in the table were semiseriously sectioned



Fig. 3 Higher magnification of Fig. 2 disclosing the detail of the structure of the myomatous nodule and the wall of the vein (Trichrome $\times 700$)

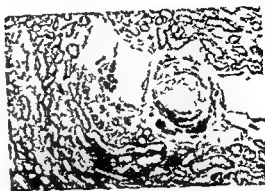


Fig. 5 The neurovascular complex deeper in the parenchyma of the kidney showing a collection of the eccentric longitudinal muscle fiber adjacent to the vein (Trichrome $\times 40$)



Fig. 4 The neurovascular complex in the parenchyma of the kidney. Note the artery on top (A), two large nerve bundles (N) below the artery with a few small veins on the left side of the photograph. Longitudinal muscle bundles (darker in color) are noted in the lower part of the picture. Fibrous and hyaline areas (H) are also noted (Trichrome $\times 40$)



Fig. 6 Arrangement of the longitudinal muscle fibers near the veins indicated in this photograph deep in the parenchyma of the kidney (Hematoxylin and eosin $\times 40$)

numbered in sequence and processed for microscopic examination they disclosed no regular parallel or spiral pattern for eccentric longitudinal muscle fibers. It appears that these muscle fibers are interrupted and patchy rather than continuous.

In the animal experiment part of the study (Table I) the rats of various age groups as well as those made arteriosclerotic and prostatic by Selver's dihydrotrichsterol method showed no evidence of longitudinal muscle fibers which could be identified by light microscopy in either the adrenal or kidney. Fibrous tissue however is present near the hilum of the kidney surrounding the neurovascular complex entering the organ.

No association was found between the high blood pressure and the presence of

hypertrophic longitudinal muscle fibers of the adrenals and kidneys.

Discussion

Concentric longitudinal muscle fibers are present in the wall of many veins including the renal veins. Aside from these in the neurovascular complex entering the hilum of the kidneys many longitudinal muscle fibers are noted which are irregularly distributed. Most of them however are near or adjacent to the smaller veins which have thin walls. Extension of these muscle fibers into the parenchyma of the kidney is noted along with the branching of the neurovascular complex. Deeper in the parenchyma where isolated small veins are noted fairly frequently one recognizes the presence of interrupted eccentric longitudinal muscle



Fig. 7 Marked hypertrophy of the muscle fibers is noted in the wall of a vein near the periphery of the kidney (Trichrome $\times 200$)



Fig. 9 Higher magnification of Fig. 8 discloses the finer structure of the muscle bundle and the wall of the vein (Trichrome $\times 200$)



Fig. 8 An almost collapsed vein (1) noted near the top of the photograph with bundles of hypertrophic longitudinal muscle fibers adjacent to it. Some of the muscle fibers extend to a second vein (2) on the right upper corner of the picture. (Trichrome $\times 40$)



Fig. 10 A small vein (1) noted in the left upper corner of the photograph with three groups of eccentric longitudinal muscle fibers, one of which is protruding into the lumen (Trichrome $\times 40$)

fibers adjacent to the wall of the veins but they are not seen near the arteries or elsewhere. In occasional sections some of the fibers of the longitudinal musculature are noted extending from one small vein to the next. The muscle fibers are noted infrequently at the periphery of the kidney parenchyma, but always adjacent to a small vein. The function of these fibers in the kidney is not known.

The presence of the longitudinal muscle fibers along the course of the central adrenal veins has been known for some time.¹ It should be noted, however, that these eccentric muscle bundles both in the adrenal and kidney are not continuous but interrupted and patchy. They are also found not only in the medulla of the adrenal but occasionally in the adipose tissue adjacent to the gland.

In regard to the function of these muscle fibers it has been postulated by some that they control the blood flow and the hormonal output of the adrenal.² Others have suggested that they function as a valve.³ We feel that the latter hypothesis is more plausible since the fibers are interrupted.

It has been said that the longitudinal muscle fibers are present in the adrenal of adult humans.⁴ Following our study we feel that it is more precise to say that such longitudinal muscle fibers do not exist at the time of birth and they are not seen in infants. They are, however, present in children but not as frequently as they are seen in adults.

Ox and other mammals have been said not to show eccentric longitudinal muscular development in the veins of the adrenal.⁴ Another study suggests that such muscle



Fig. 11 The same vein as in Fig. 10 is demonstrated in the right upper corner of the photograph with detailed structures of the vein and the muscle fibers (Trichrome $\times 200$)

fibers in the suprarenal glands are less developed in mammals other than man.⁸ In our study of the adrenals and kidneys of rats we did not find any eccentric longitudinal muscle fibers regardless of the age of the animals.

Association of the hypertrophy of the longitudinal muscle fibers in the central adrenal veins with hypertension was noted by Goldzieher and Sherman.⁸ Such a relationship however has not been confirmed by this or any other study as far as we know. The muscle fibers are not present in the newborns and infants. They appear during the childhood and increase in number gradually in later life. Therefore their development could be related to sex hormones and maturity. Nodular hypertrophy and particularly fibrosis of these muscle bundles in later life has been called micronodular phlebosclerosis.⁹ We prefer to assume that such a process could be related to age and stress⁷ rather than a specific disease entity such as hypertension.⁸

Summary

A large number of sections were taken from adrenals and kidneys of human subjects of various age groups. The sections

were stained by hematoxylin and trichrome methods and they were examined for presence or absence of interrupted eccentric longitudinal muscle fibers along the course of the veins. It is noted that these muscle fibers are absent in newborns and infants; they are present in small amounts in children and they increase with age. The fibrous tissue particularly is noted to increase as age advances. These are more easily found in the adrenals than they are in the kidneys. In older people focal hypertrophy and fibrosis of these muscle bundles could form a nodular pattern occluding the lumen of the veins. It appears to us that hypertrophy and fibrosis of these muscle fibers are related to old age and stress rather than to a particular disease process such as hypertension. Examination of the adrenals and kidneys of rats showed no evidence of longitudinal muscle fibers.

Appreciation is expressed to Isabel Knucely Ann Sharpe and Sandra Phillips for their assistance.

REFERENCES

- 1 Ham A. Histology ed 6 J B Lippincott Co Philadelphia 1969 pp 601-607
- 2 Furston J. The veins of the adrenal. *Am J Anat* 5:63 1906
- 3 Goldzieher M and Sherman J. Hypertrophy of muscles of suprarenal vein in hypertension. *Arch Pathol* 5:1 1978
- 4 Franklin J. A monograph on veins ed 1 Baltimore 1937 C C Saunders Co pp 108-114
- 5 Goldzieher M. The adrenal glands in health and disease ed 1 Philadelphia 1944 David Co pp 19-21
- 6 Symington T. Morphology and secretory cytology of the human adrenal cortex. *Br Med Bull* 18:117 1962
- 7 Payan H M and Gilbert H. Micronodular phlebosclerosis. An inter-arteriole change of the venules of the kidney and adrenal. *Angiology* 18:1381 1967
- 8 Strebel R, Payan H and House L. Sex differences in progeria like syndrome. *Proc Soc Exp Biol Med* 117: 583 1964
- 9 Selye H, Goldie I and Strebel R. Effect of anabolic hormones and ferric dextran upon the progeria like syndrome produced by dihydrocholesterol. *Gerontologia* 7:94 1963



Fig 7 Marked hypertrophy of the muscle fibers is noted in the wall of a vein near the periphery of the kidney (Trichrome $\times 200$)



Fig 9 Higher magnification of Fig 8 discloses the finer structures of the muscle bundle and the wall of the vein (Trichrome $\times 200$)



Fig 8 An almost collapsed vein is noted (V) near the top of the photograph with bundles of hypertrophic longitudinal muscle fibers adjacent to it. Some of the muscle fibers extend to a second vein (V) on the right upper corner of the picture (Trichrome $\times 40$)

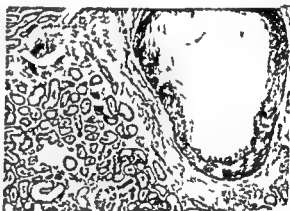


Fig 10 A small vein is noted in the left upper corner of the photograph with three groups of eccentric longitudinal muscle fibers one of which is protruding into the lumen (Trichrome $\times 40$)

fibers adjacent to the wall of the veins but they are not seen near the arteries or elsewhere. In occasional sections some of the fibers of the longitudinal musculature are noted extending from one small vein to the next. The muscle fibers are noted infrequently at the periphery of the kidney parenchyma but always adjacent to a small vein. The function of these fibers in the kidney is not known.

The presence of the longitudinal muscle fibers along the course of the central adrenal veins has been known for some time.^{1,2} It should be noted, however, that these eccentric muscle bundles both in the adrenal and kidney are not continuous but interrupted and patchy. They are also found not only in the medulla of the adrenal but occasionally in the adipose tissue adjacent to the gland.

In regard to the function of these muscle fibers it has been postulated by some that they control the blood flow and the hormonal output of the adrenal.³ Others have suggested that they function as a valve.⁴ We feel that the latter hypothesis is more plausible since the fibers are interrupted.

It has been said that the longitudinal muscle fibers are present in the adrenal of adult humans.⁴ Following our study we feel that it is more precise to say that such longitudinal muscle fibers do not exist at the time of birth and they are not seen in infants. They are however present in children but not as frequently as they are seen in adults.

Ox and other mammals have been said not to show eccentric longitudinal muscular development in the veins of the adrenal.⁴ Another study suggests that such muscle

sixth intercostal space. The ends of the nylon snare were passed through the tube the flared end of which was sutured to the pericardium (Fig 1). The tube was then filled with petroleum jelly to form an air seal. The pericardium was sutured and the implanted probe wires and left atrial catheter were brought through the chest at the posterior end of the incision and the thorax was closed. During surgery a slow continuous intravenous drip of 5 per cent dextrose in water was maintained and whole blood from donor rhesus monkeys was transfused according to the blood loss. Mephentermine sulfate (1 mg) (Wyamine—Wyeth Laboratories Inc) was given intravenously if the blood pressure dropped below normal levels especially after dissection around the aorta and placement of the flow probe. After surgery 1 000 000 units of benzathine penicillin and procaine penicillin G (Bicillin CR—Wyeth Laboratories Inc) were given intramuscularly. The monkey was then placed in a specially designed suit to recuperate in a cage for 3 to 5 days.

On the morning of occlusion the animal was placed in a restraining chair and electrocardiographic (ECG) electrodes were sutured to the proximal part of the four limbs and to three chest positions (V_1 and V_2 were 1 cm below the right and left mammary papilla respectively, V_3 was placed 1 cm lower than V_2 and at the anterior axillary line). Blood pressure transducers were placed at the level of the heart and 4 to 6 recordings at 15 minute intervals were averaged for the control values. After a steady state had been reached the snare was gradually tightened over a period of 1 to 2 minutes while the ECG was constantly monitored on a 3 channel oscilloscopic recorder (Sinhorn Model 350). Tension on the snare with counterpressure on the tubing produced complete occlusion of the artery. The expected end point was indicated by an injury current (ST segment elevation) in any of the precordial leads. At appropriate intervals the following parameters were recorded: (1) 9 leads ECG (2) blood flow in the ascending aorta (considered to represent cardiac output when coronary flow is disregarded) (3) left atrial pressure (4) aortic systolic diastolic mean and pulse pressure and (5) heart rate.

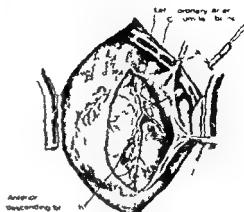


Fig 1 Drawing of midline sternotomy exposing pericardial cavity and illustrating the location of the snare used to produce myocardial infarction. SVC = superior vena cava, Ao = aorta, LA = left coronary artery.

After infarction recordings were taken at 5 minute intervals for 1 hour, 10 minute intervals for 1 hour, 30 minute intervals for 2 hours and 1 hour intervals thereafter during each working day. The monkeys were continuously observed until 5 P.M. and recordings were taken of any significant changes. The animals were then periodically observed until midnight but no recordings were made after 5 P.M. External defibrillation with direct current countershock (American Optical Co) at 200 watt seconds was applied if serious ventricular arrhythmias (ventricular tachycardia, flutter or fibrillation) were present. When the animals died or when the experiments were terminated 24 to 98 hours after infarction necropsies were performed to verify the position of the snare and the size and location of the infarction.

For prediction of clinical outcome we used discriminant analysis¹⁹ based on the general formula:

$$L = K + aW + bV + cI + dZ$$

where L = discriminant function, K = constant, a = coefficient for aortic systolic blood pressure, W = coefficient for aortic diastolic blood pressure, V = coefficient for aortic mean blood pressure, I and

Experimental myocardial infarction in unanesthetized monkeys*

John D. Hull, D.V.M., M.Med.Sci.

Manuel A. Malinova, M.D.

Wilbur P. McNulty, M.D.

† John Ochsner, III, B.S.

Beaverton and Portland, Ore.

The literature on experimental myocardial infarction in monkeys is very limited.¹⁻⁶ Most studies in the past have used species other than nonhuman primates such as the dog,⁶⁻¹⁰ and pig.¹¹ Moreover, the observations were made mainly on acute preparations performed under various types of anesthetics.¹⁻³ Recently several reports have described methods of producing coronary occlusion in conscious dogs.¹²⁻¹⁴ This investigation was undertaken to study cardiovascular changes in unanesthetized monkeys from the moment myocardial infarction was induced.

Methods

The experimental animals were 12 male and 22 female adult *Macaca mulatta* weighing between 4.5 and 9.5 kilograms. Twenty mg of succinylcholine chloride (Quelcin Abbott) were administered intravenously and a cuffed endotracheal tube was inserted. General anesthesia 0.5 to 1.25 per cent halothane (Fluothane Ayerst) vapor

ized in a Fluotec vaporizer with 40 per cent nitrous oxide and 60 per cent oxygen was administered with a Boyle's anesthetic machine.

A polyvinyl catheter was implanted in the aorta via the femoral artery and was connected to a transducer (Statham Model p23Db) to monitor blood pressure during surgery and during the ligation experiment several days later. After the thorax had been opened by a midline sternotomy, an electromagnetic square wave flow probe (Biotronex Laboratories) was placed around the aorta just superior to the coronary arteries. A polyvinyl catheter was placed in the left atrial appendage by means of a purse string suture. A nylon filament suture (8 lb test nylon swaged on a needle) was passed through the pericardium and loosely placed around the left anterior descending coronary artery 2 or 3 mm distal to the origin of the circumflex branch. By means of a stab incision a polyvinyl tube with a flared tip was passed through the left

From the Departments of Surgery, Cardiology and Physiology of the Oregon Regional Primate Research Center, Beaverton, Ore., and the Departments of Medicine and Pathology of the University of Oregon Medical School, Portland, Ore.

Supported by Contract 111-41-69-686 from the Artificial Heart Research Institute, Portland, Ore., and by grant 1R01-HE-00163 from the National Institutes of Health.

Received for publication Aug. 30, 1971.

Reprint requests to Dr. John D. Hull, Oregon Regional Primate Research Center, 505 N.W. 145th Ave., Beaverton, Ore. 97005.

*This is publication No. 565 of the Oregon Regional Primate Research Center.

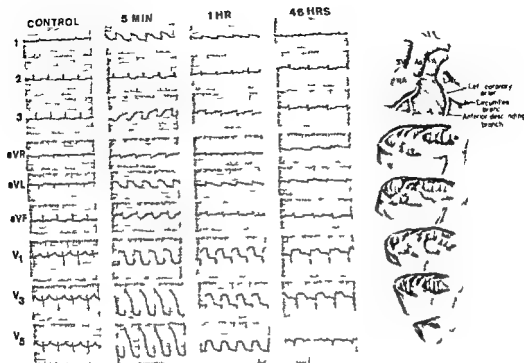


Fig. 3 Serial electrocardiograms with drawing of heart illustrating a more extensive area of infarction than in Fig. 2

Immediately after the snare was pulled the animals became agitated for 1 to 2 minutes. In general those animals with initial decreases greater than 50 per cent in aortic blood flow and 30 per cent in mean aortic pressure appeared dazed, did not respond immediately to external stimuli, did not eat or drink, did not survive longer than 61 hours after myocardial infarction and presumably died from cardiogenic shock. The animals that survived the infarction more than 12 hours remained alert and responsive to their environment and ate and drank normally.

Electrocardiogram Immediately after the obstruction of the left anterior descending coronary artery, the ST segment became slightly elevated in Leads I, aVL, and the precordial leads and depressed in Leads II, III, and aVF. The rapid increase in ST displacement became marked (several mm) 3 to 4 minutes later (Fig. 2). About 30 minutes after ligation a small Q wave appeared in the standard leads and in Leads aVR and V1 and increased in amplitude. A QS pattern developed in the precordial leads. Twenty-four hours later the ST

displacement tended to disappear in the frontal plane but remained elevated in the precordial leads. The QS pattern persisted in the animals that survived for 4 days after the occlusion procedure. This pattern corresponding to infarction of the anterior and part of the lateral wall of the left ventricle, the anterior half to two thirds of the septum, and a small portion of the anterior right ventricular wall was determined by postmortem examinations. A slightly different ECG pattern was observed in two animals that had left ventricular necrosis extending much farther laterally than was general (Fig. 3) and in another monkey with a small and strictly lateral infarction of the left ventricular wall (Fig. 4).

Right bundle branch block (RBBB) was observed in 13 animals after snare ligation. The conduction defect apparently did not affect survival and occurred about equally in both the alive and dead groups. In most cases it was evident in the one hour recording after infarction; however, a few animals did not develop RBBB for several hours. RBBB was present in one monkey one hour after ligation but had disappeared

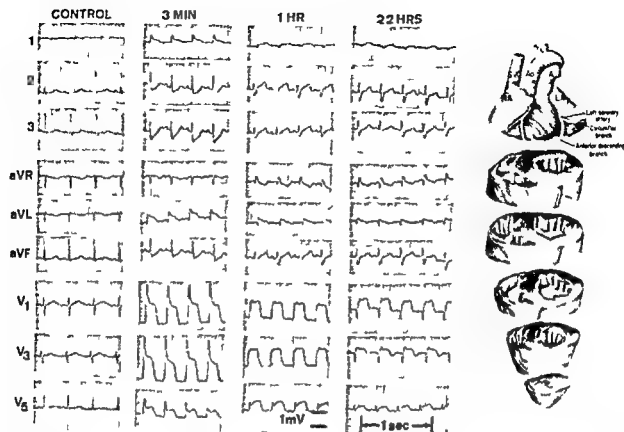


Fig 2 Serial electrocardiograms with drawing of heart illustrating area of infarction typically found after ligation of the left anterior descending coronary artery in the monkey. In this animal right bundle branch block was also present after infarction. In these and the following figures the ECG was standardized at 1 cm per millivolt and the paper speed was 50 mm per second.

d = coefficient for aortic mean blood flow Z . At selected periods after ligation (see *Results* below) values were obtained from all monkeys for systolic, diastolic and mean blood pressure and for aortic flow. With these data and a program written in Fortran II and executed on a Xerox Data System Model 920 digital computer, the constant and coefficients were determined for the "alive" and "dead" groups separately. The pressures and flows from individual animals were then used with the previously generated constant and coefficients from each group. This produced an L_1 and L_2 function for every individual. Monkeys whose L_1 was larger than L_2 were predicted to survive retrospectively. The retrospective predictions were compared with the observed events to determine the per cent of accuracy.

Results

Five of the 34 animals undergoing surgery died postoperatively before ligation. The 29 survivors had the snare ligated, in

3 of these the ligation was unsuccessful because misplacement of the snare excluded the coronary artery or included part of the pulmonary valve, or the snare broke. The remaining 26 were divided into two groups: (1) Group I ('dead') comprised the 11 monkeys that died within 6½ hours from myocardial infarction with a syndrome resembling cardiogenic shock; and (2) Group II ('alive') comprised the 15 monkeys that survived myocardial infarction more than 12 hours and in many cases were killed 24 to 98 hours after infarction. No deaths occurred in the interval between 6½ and 12 hours after infarction. Five animals that died during the night but more than 12 hours after infarction may have had cardiogenic shock; however the possibility of a fatal arrhythmia cannot be ruled out. Since their aortic blood flow was never under 55 per cent (percentages refer to control values taken as 100 per cent), and mean aortic pressure never was less than 70 per cent during the observed period they were placed in Group II.

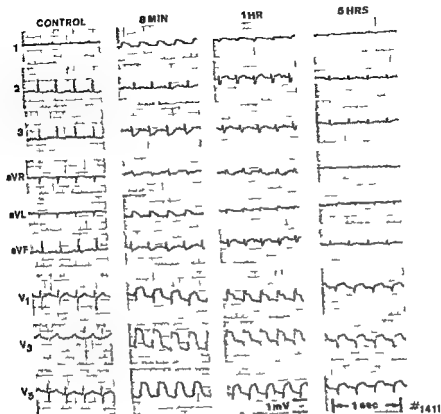


Fig. 5 After infarction transient right bundle branch block was apparent in the one hour tracing but had disappeared by the time of the 5 hour tracing

complete A V block with idioventricular rhythm (Fig 7 C) the atrial rate was 210 beats per minute and the ventricular rate was 10 beats per minute. The aortic blood pressure was 90/50 mm Hg. About 12 hours later (Fig 7 D) the arrhythmia changed to first-degree A V block with a P R interval of 0.13 seconds (in a study of 351 *Macaca mulatta*⁴⁹ the P R interval was 0.07 ± 0.01 sec) the heart rate was 100 beats per minute and the aortic blood pressure was 110/60 mm Hg. The monkey remained alert and ate well when it was finally killed 98 hours after the myocardial infarction the first-degree A V block was still present and the heart rate and blood pressure were unchanged. The possibility of second-degree A V block was considered because a T wave could be buried in the T wave but this could not be confirmed.

Hemodynamics. The Group I animals displayed severe hemodynamic changes immediately after coronary ligation and a

partial blood pressure recovery about 1 hour after ligation (Fig 8). They also showed wider and more frequent variations than the Group II animals. In general the aortic flow (cardiac output minus coronary flow) dropped from the 100 per cent control value to 45 per cent shortly after coronary ligation. Although the flow fluctuated generally it did not rise above 50 per cent of the control value throughout the survival period. Immediately after occlusion the aortic mean blood pressure fell to about 60 per cent of the control values slowly rose in some cases to within 75 per cent of the control values about 1 hour after ligation and then progressively declined until death.

The hemodynamic changes were less severe in Group II animals than in Group I animals. The aortic flow dropped immediately after coronary ligation to about 65 per cent of the control values but generally never below 55 per cent at any time during

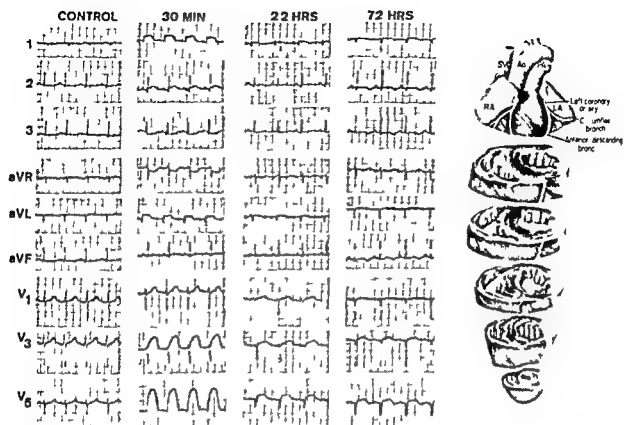


Fig. 4 Serial electrocardiograms with drawing of heart from monkey No. 19 with a lateral myocardial infarction

by the 7 hour tracing (Fig. 5). In another animal (Fig. 6) presurgery tracings illustrated different degrees of RBBB; after surgery but before ligation the block was incomplete and the alteration had ceased; more complete degrees of RBBB were observed in the two tracings after suture ligation.

Premature ventricular beats were common immediately after coronary occlusion but the most serious and frequent arrhythmia was ventricular fibrillation, one to 9 episodes of which occurred in 18 animals. Ventricular fibrillation was noted in 2 animals about 24 hours after ligation; the other 57 episodes were observed within 40 minutes after coronary occlusion. These arrhythmias were successfully terminated with d.c. countershocks delivered with external paddles at 200 watt seconds. Ventricular fibrillation did not appear to affect survival; 35 episodes occurred in 11 of the 15 (73 per cent) monkeys in Group II and 24 episodes occurred in 7 of the 11 (63 per cent) animals of Group I. In two instances a recorded arrhythmia could have been

counted for the death of one animal in each group.

Ventricular fibrillation and ventricular premature beats were the only arrhythmias observed during the first hours after the infarction; other complex arrhythmias were observed later on. Twenty-two and one-half hours after myocardial infarction a bigeminal rhythm in monkey No. 18 was followed shortly by spontaneous recovery to normal sinus rhythm. The aortic blood pressure during the arrhythmia was about 80/35 mm Hg, which rose to 120/80 when the arrhythmia converted. Serious arrhythmia is also observed in the animal kept alive the longest. About 25 hours after coronary ligation either ventricular tachycardia or flutter at a rate of 430 to 500 beats per minute was observed in monkey No. 17 (Fig. 7 A); the aortic mean blood pressure fell to about 50 mm Hg. This arrhythmia was quickly followed by ventricular fibrillation which was successfully defibrillated by d.c. countershock; after defibrillation the aortic blood pressure was 110/65 mm Hg (Fig. 7 B). Forty-six hours after myocardial infarction this animal had

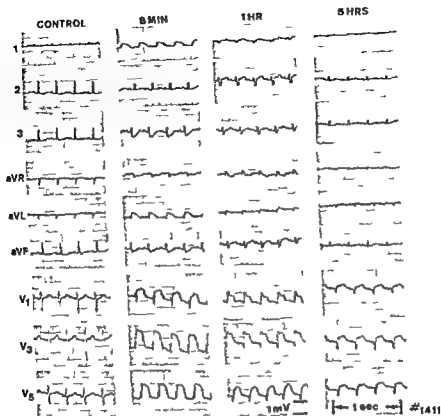


Fig. 5 After infarction transitory right bundle branch block was apparent in the one hour tracing but had disappeared by the time of the 5 hour tracing.

complete A-V block with idioventricular rhythm (Fig. 7 C) the atrial rate was 21½ beats per minute and the ventricular rate was 10 beats per minute. The aortic blood pressure was 95/50 mm Hg. About 1½ hours later (Fig. 7 D) the arrhythmia changed to first degree A-V block with a P-R interval of 0.13 seconds (in a study of 351 *Macaca mulatta* the P-R interval was 0.07 ± 0.01 sec) the heart rate was 100 beats per minute and the aortic blood pressure was 110/60 mm Hg. The monkey remained alert and ate well when it was finally killed 98 hours after the myocardial infarction the first-degree A-V block was still present and the heart rate and blood pressure were unchanged. The possibility of second-degree A-V block was considered because a P wave could be buried in the T wave but this could not be confirmed.

Hemodynamics. The Group I animals displayed severe hemodynamic changes immediately after coronary ligation and a

partial blood pressure recovery about 1 hour after ligation (Fig. 8). They also showed wider and more frequent variations than the Group II animals. In general the aortic flow (cardiac output minus coronary flow) dropped from the 100 per cent control value to 45 per cent shortly after coronary ligation. Although the flow fluctuated generally it did not rise above 50 per cent of the control value throughout the survival period. Immediately after occlusion the aortic mean blood pressure fell to about 60 per cent of the control values slowly rose in some cases to within 75 per cent of the control values about 1 hour after ligation and then progressively declined until death.

The hemodynamic changes were less severe in Group II animals than in Group I animals. The aortic flow dropped immediately after coronary ligation to about 60 per cent of the control values but generally never below 50 per cent at any time during

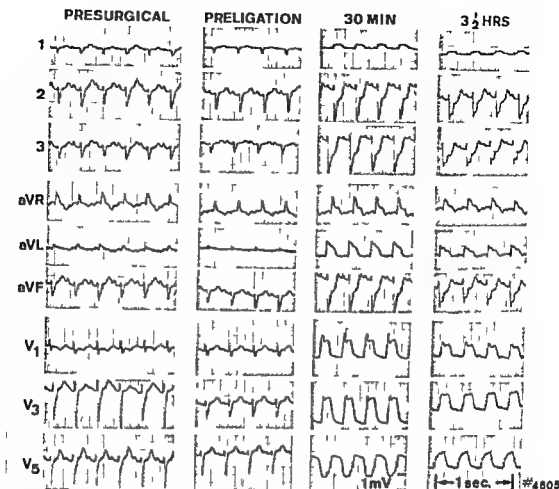


Fig 6 Presurgery tracings illustrate different degrees of right bundle branch block (RBBB) alternately. After surgery but before ligation the block was incomplete and the alternation had ceased. More complete degrees of RBBB were observed in the two tracings after snare ligation.

the experiment. Initially, the aortic mean blood pressure fell to about 75 per cent of the control values. Afterwards it rose earlier and more rapidly than in Group I animals to about 80 to 85 per cent of the control values and remained relatively stable thereafter.

In the early postinfarction period there was considerable overlapping between Group I and Group II animals in heart rate and in mean left atrial pressure. In the later stages the mean left atrial pressure in Group II animals tended to remain elevated but showed a steady decline in Group I animals.

Since systolic/diastolic and electronic mean blood pressures had been recorded during the experiments we decided to use this somewhat artificial division into three components along with the flow measurements to develop a computer program for discriminant analysis for future experi-

ments in our laboratory. We analyzed several arrangements of the data by selecting the pressure and flow measurements for each animal at certain time periods after infarction (10, 15, and 30 minutes), by selecting an average value for the pressure and flow measurements from several recordings during the first 30 minutes after infarction or by selecting the data for each animal at the time of its lowest systolic, diastolic mean or flow measurements during the first 30 minutes after infarction. In all cases the preceding data arrangements were analyzed by expressing the blood pressure values in mm Hg and by expressing them as a percentage of the animal's own control value and by including or excluding the flow measurements. The best arrangement was to select the blood pressure and flow measurements for each animal at the time of its lowest diastolic blood pressure recording during the 30 minute

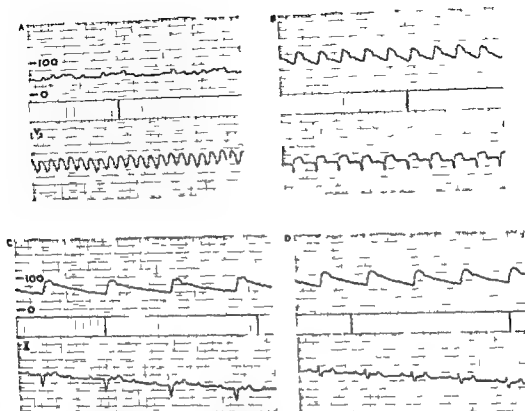


Fig 7 A through D Tracings from monkey No. 17 A About 25 hours after coronary ligation either ventricular tachycardia or flutter at a rate of 430 to 500 beats per minute was observed. The aortic mean blood pressure was about 50 mm. Hg. This arrhythmia was quickly followed by ventricular fibrillation. B After successful defibrillation by d.c. countershock the aortic blood pressure was 110/65 mm Hg. C Forty six hours after infarction complete heart block was present with an atrial rate of 215 and a ventricular rate of 70 beats per minute. The aortic blood pressure was 95/50 mm Hg. D About 1 1/2 hours later the arrhythmia changed to first-degree heart block with a P R interval of 0.13 seconds. The heart rate was 100 beats per minute and the aortic blood pressure was 110/65 mm. Hg and remained unchanged until the animal was finally killed 98 hours after myocardial infarction.

postligation period with blood pressure values expressed in mm Hg. Retrospectively this data arrangement correctly predicted 100 per cent (11 out of 11) of the monkeys dying from myocardial infarction with shock and 93 per cent (14 out of 15) of the monkeys surviving for more than 12 hours. Statistical analyses of the hemodynamic data used in this arrangement are given in Table I. After the experimental coronary occlusion blood pressure measurements and aortic flow fell significantly ($p < 0.001$) in both groups of animals. The largest decrease after infarction occurred in the aortic flow which in Group I dropped 63 per cent and in Group II fell 38 per cent. The two groups did not differ significantly in their control values however

after myocardial infarction they differed significantly.

The other data arrangements did not predict so accurately the arrangements that included aortic blood flow were more accurate than those without it but predictions based on flow measurements alone were even less accurate. Arrangements using values at a fixed time period after the infarction or each animal's average value from several recordings taken immediately after the infarction were also less accurate.

Pathology A complete postmortem examination was performed on each animal. After the intact heart had been fixed for several days the ligation site was dissected under the microscope for verification of

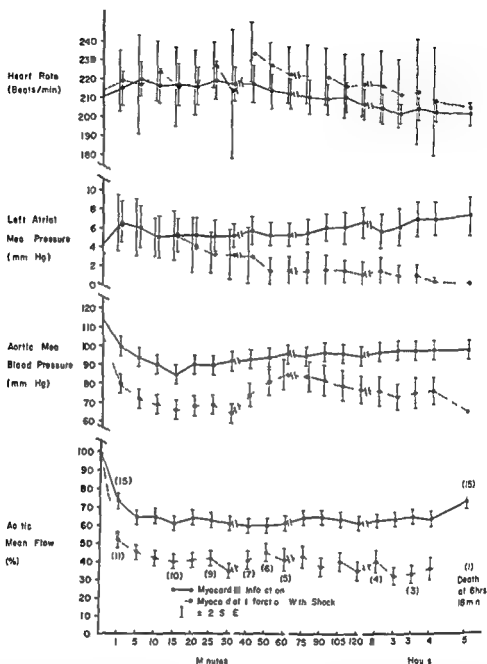


FIG. 8. Aortic blood pressure and mean flow illustrating a critical time period that occurred in the first 30 minutes after myocardial infarction followed by a partial recovery period and subsequent progressive deterioration for the cardiogenic shock group. Numbers within parentheses indicate the number of animals used for mean and standard error at that time period.

placement of the snare. Then the heart was cut in horizontal slices 3 to 5 mm thick from the apex to the A-V sulcus usually 9 to 11 slices per heart. A full microscopic section was made from each paraffin embedded slice and stained with hematoxylin and eosin.

Group I. Death occurred too early for anatomical changes of infarction to be seen in these animals, although occlusion of the left anterior descending coronary artery

was demonstrated. Various degrees of renal tubular necrosis were found in 5 monkeys. The histological changes ranged from patchy areas of coagulation necrosis of convoluted tubules with occasional neutrophilic casts and early regeneration to wedge shaped areas of cortical necrosis in one monkey. Two of these animals also had histological evidence of anoxic parenchymal necrosis in the liver and splenic infarcts. In some cases these visceral ne-

Table I Comparison of hemodynamic data employed in discriminant analysis

Variables	Group I (dead)		Group II (alive)		Group I versus Group II	
	Control (Mean \pm SD)	Postinfarction (Mean \pm SD)	Control (Mean \pm SD)	Postinfarction (Mean \pm SD)	Control I	Postinfarction I
Aortic systolic b.p.	147 \pm 12	81 \pm 9†	154 \pm 27	107 \pm 27†	NS	< 0.01
Aortic diastolic b.p.	111 \pm 10	47 \pm 7†	95 \pm 18	63 \pm 19†	NS	< 0.01
Aortic mean b.p.	109 \pm 11	60 \pm 8†	115 \pm 20	81 \pm 20†	NS	< 0.01
Aortic mean flow (%)	100	37 \pm 6†	100	67 \pm 14†	—	< 0.001

b.p. = blood pressure mm Hg

† Significant difference from control, $p < 0.001$, t test

SD = standard deviation

NS = non-significant

† = not possible to determine

crosses were clearly older than the post infarction time

Group II At about 14 hours after infarction no gross evidence of an infarct was seen. Histological sections showed increased cytoplasmic eosinophilic smudging of cross striations and shrinkage of nuclei. At 24 hours the infarction was characterized grossly by an area of vague pallor; the histological signs were confined to cell shrinkage, loss of nuclei, edema and minimal marginal leukocytic infiltration. By 48 hours the infarct was grossly visible below the snare as an irregularly shaped area of gray discoloration. At this time there were histological signs of massive necrosis with peripheral leukocytic infiltration. A zone of neutrophils marked the boundary of the infarct by 72 hours but organization had not yet begun. At 96 hours the complete central necrosis was bordered by a band of largely necrotic neutrophils and numerous zones of young granulation tissue.

The distribution of necrosis in these animals was fairly constant; nearly all of the apex was involved and higher sections up to the level of the ligation showed necrosis in the anterior and part of the lateral wall of the left ventricle, the anterior half or two thirds of the septum and a small portion of the anterior right ventricular wall. Generally a narrow zone of subendocardial muscle remained viable. However in monkey No 17 the necrosis extended to the ventricular lumen and mural thrombus was attached. Thrombi were found in the renal arteries presum-

ably embolic from the heart. Thrombi were not found in the anterior descending coronary artery below the point of ligation. This is also the only animal that was kept alive until 98 hours after ligation; other animals were usually killed 48 hours after infarction. Two animals had left ventricular necrosis extending much farther laterally than was general in one monkey. Anomalous duplicate anterior descending coronary arteries had been included in the snare in the other monkey; the artery was unusually large (Fig. 3). A small and strictly lateral infarction of the left ventricular wall was found in animal No 19 (Fig. 4). In this animal the snare did not include the anterior descending artery but its close proximity to the origin of the circumflex branch may have resulted in reduced blood flow caused by compression of the surrounding tissue.

Various degrees of renal tubular necrosis were found in 5 monkeys, 3 of which also had evidence of anoxic paracentral necrosis of the liver. Renal infarcts were found in 6 animals, 2 of which also had necrosis of the zona reticularis of the adrenal gland. The one case of hepatic vein thrombosis was of unknown origin. Again in some cases these lesions were clearly older than the postinfarction time.

Discussion

Reports of spontaneous myocardial infarction are rare in nonhuman primates^{1,2} and the literature on experimental myocardial infarction in them is also very limited.^{1,2} The most extensive use of non

hum in primates was made by de Wurt and co workers³ who described ECG changes after ligation of either the left anterior descending or the right coronary artery in 31 animals (*Macaca irus*). The present study contributes electrocardiographic and hemodynamic data in unanesthetized, chair restrained rhesus monkeys.

Many different methods have been used to induce experimental myocardial infarction in several species including variations of snare devices in open chest¹ or closed chest animals^{16, 17} and snares occluded by remote radio control.⁵ Coronary artery occlusion has been achieved by thrombus formation after direct electrical current applied to an electrode catheter^{6, 8, 12} and by balloon cuffs^{11, 18} or Ameroid constrictors.¹⁹ Other methods have produced coronary artery obstruction by embolism.^{7, 10, 13, 14} In man 70 per cent of coronary artery occlusions occur within 3 to 4 cm of the coronary ostia.²⁰ In our study the snare of nylon swaged on a needle causes little trauma to the heart and allows direct visualization and placement on the proximal region of the coronary artery. Although this method does require preparative surgery it does not need fluoroscopic equipment nor the use of anesthetics on the day of ligation. Most of the closed chest methods require some surgical manipulation under anesthesia immediately before creation of the infarction. The anesthetic agent itself may have a direct depressant effect on the myocardium and may produce marked changes in the cardiovascular system²⁰ or it may modify neurohumoral mechanisms that determine circulatory system responses to severe myocardial trauma.^{21, 22}

Because of the tractable nature and ease of training dogs studies with continuous monitoring devices are possible in these animals without anesthesia or restraining devices.^{11, 18} Unfortunately, in most studies aggressiveness and the difficulty of training nonhuman primates make it necessary to use some type of plastic restraining chair as we did. However, this partial restriction of the animal in the sitting position may introduce hemodynamic factors not found for instance in man in the supine position.

Ventricular fibrillation is an early and frequently observed event after acute coro-

nary occlusion.^{8, 12, 13, 23} In one study^{8, 24} out of 57 (79 per cent) dogs experienced episodes of ventricular fibrillation within the first hour after infarction. In monkeys the chance of fibrillation after ligation was found to be greatest during the first 40 minutes.²⁴ Although many drugs have been studied for their antiarrhythmic activity,²⁵ their use complicates the evaluation of experimental myocardial infarction. In dogs ventricular fibrillation did not occur when ligation of the coronary artery was accomplished slowly in two stages²⁵ or when a balloon cuff was inflated slowly.¹¹ Multiple episodes of ventricular fibrillation in the same animal have not been reported. In our study where an external defibrillator and continuous ECG monitoring were available, 15 of 18 monkeys experienced more than one episode of ventricular fibrillation usually within 40 minutes after infarction. These episodes occurred about equally between the survivors and non survivors. Moreover complex arrhythmias other than ventricular fibrillation did not develop until several hours after the coronary occlusion. This has also been reported by other investigators.^{13, 18}

An increased heart rate has been described after experimental infarction.^{14, 18} Little difference occurred in our study where the control heart rates and blood pressures were also higher than those reported in chronically chair restrained rhesus monkeys.⁸ The animals probably had not reached base line values before the experiment started. Although an average of 4 preligation recordings were made during a 1 to 2 hour control period, no special precautions had been taken. Conditioning to the restraining chair and isolation might be considered useful adjuncts to the experiment.

Because death occurred too early for histological changes of myocardial infarction to be observed in Group I monkeys, no comparison of the infarcts could be made with Group II; however the ECGs were similar. Anatomical changes in the kidney ranged from necrosis of scattered groups of tubules to wedge shaped areas of cortical necrosis. The latter may have been simple infarcts from catheter emboli that were not found although the glomeruli were usually spared. No relationship be-

tween renal tubular necrosis and blood administration during surgery was found. The renal damage may have been related to hypotension during surgery, especially after dissection around the aorta and placement of the flow probe. In animals that survived surgery 5 days or more, early tubular regeneration was frequently noted. How much some degree of impairment of kidney function contributed to later deaths could not be ascertained; a more detailed study of renal function would be needed. More renal lesions (and the only adrenal lesions) were found in Group 11 (alive) monkeys than in Group I (dead) monkeys.

Cardiogenic shock is a grave complication of myocardial infarction and usually carries a mortality rate of about 80 per cent in man.^{24,27} Although much has been written about it,^{28,29} precise definitions are difficult. Criteria reported by some investigators^{12,13} for experimental cardiogenic shock include: (1) a fall in mean arterial pressure of at least 30 per cent with no recovery for at least 30 minutes; (2) ECG evidence of severe ischemia with no arrhythmias to account for the fall in blood pressure; and (3) initial reduction of the cardiac output by 50 per cent. In Group I animals, the aortic flow (cardiac output minus coronary flow) initially dropped to 45 per cent and generally did not rise above 50 per cent throughout the survival period. After a marked decrease, the mean aortic pressure did not rise above 75 per cent of the control value in the survival period. Furthermore, all these animals died within 61 hours after myocardial infarction, and we feel that the definition of cardiogenic shock can be sustained.

Retrospectively, by means of discriminant analysis and based on information obtained within 30 minutes after infarction, the death or survival of 25 out of the 26 animals was accurately predicted. With the computer program, other parameters could easily be added rather than the somewhat artificial division of blood pressure, and these parameters could be used in a prospective rather than in a retrospective study. A model of myocardial infarction in unanesthetized monkeys with an early prediction of death or survival may allow time for studies on the therapy of cardio-

genic shock which might give some insight into this condition in man.

Summary

Experiments were undertaken to study myocardial infarction in non-human primates without the use of anesthetics or sedatives. During surgery, a snare was placed loosely around the left anterior descending coronary artery in 34 rhesus monkeys (*Macaca mulatta*). Several days later, myocardial infarction was studied from the moment it was induced. The technique was reproducible and the distribution of necrosis was fairly constant. Aortic flow, aortic blood pressure, left atrial pressure and the ECG were monitored. A computer program for discriminant analysis based on data obtained within 30 minutes after infarction resulted in retrospective predictions of 100 per cent in animals dying from cardiogenic shock and in predictions of 93 per cent in surviving animals.

We gratefully acknowledge the aid of Dr C W de Lannoy Jr and Dr Aleksander Knezevich in helping to devise some of the techniques of the earlier experiments. The authors are also indebted to Mr William Baughman, Mr I Madigan and Mr J Lindsley for technical assistance. We also wish to thank Mr D Lindgren for writing the computer program and Mr J Ito for doing the illustrations.

REFERENCES

- 1 Hirsch C and Spalteholz W. Coronararterien und Herzmuskel. *Dtsch. Med. Wochenschr.* 20: 190, 1907 (from de Waart et al.).
- 2 Sutton D C and Lueuth H C. Experimental production of pain on excitation of the heart and great vessels. *Arch. Intern. Med.* 45: 877, 1930.
- 3 De Waart A, Storm C J and Koumans A K. J. Ligation of the coronary arteries in Javanese monkeys. I. Introduction: general experimental results, especially the changes in the ventricular electrocardiogram. *Am. Heart J.* 11: 676, 1936.
- 4 Grayson J and Irvine M. Myocardial infarction in the monkey. Studies on the collateral circulation after acute coronary occlusion. *Cardiovasc. Res.* 2: 170, 1968.
- 5 Melnikov M R, de Lannoy C W, McNulty W J and Knezevich A. Continuous monitoring of myocardial infarction in nonrestrained monkeys. *Proc. Internat. Conf. Cong. of Frontiers*, Atlanta, Georgia, 1968.
- 6 Salazar A I. Experimental myocardial infarction. Induction of coronary thrombosis in

- the intact closed chest dog. *Circ Res* 9:1351 1961
7. Ilchuk S, Moskowsky H C, Pietri G, Shaffer A B, Hirsch I J and Ishman A P. A reproducible model of cardiogenic shock in the dog. *Circulation* 39:205 1969
 8. Weiss A B, Moschos C B, Pissinante A J, Khan M I and Khan T J. Relative effectiveness of three antiarrhythmic agents in the treatment of ventricular arrhythmias in experimental acute myocardial ischemia. *Am Heart J* 81:503 1971
 9. Hammer J and Liss A. A method of isolated arterial occlusion of a main branch of a coronary artery in closed chest dogs. *Am Heart J* 64:67 1962
 10. Cuzman S V, Swenson I and Mitchell R. Mechanism of cardiogenic shock. *Circ Res* 10:746 1962
 11. Hood W B Jr, Covell V H and Norman J C. Acute coronary occlusion in pigs. Effects of acetyl strophanthidin. *Circulation* 39:441 1969
 12. David M S, Charrette J J I and Lynn R B. Experimental coronary artery thrombosis for production of cardiogenic shock. *Can J Surg* 13:189 1970
 13. Agre C M, Rothenberg M J, Jacobs H I, Binder M J, Schneiderman A and Clark W G. Induced shock in the closed chest dog following coronary embolization with graded microspheres. *Am J Physiol* 170:536 1952
 14. Roos A and Smith J K. Production of experimental heart failure in dogs with intact circulation. *Am J Physiol* 153:558 1958
 15. Harris A S. Delayed development of ventricular ectopic rhythms following experimental coronary occlusion. *Circulation* 1:1318 1950
 16. Rushmer R F, Watson N, Harding D and Baker D. Effects of acute coronary occlusion on performance of right and left ventricles in intact unanesthetized dogs. *Am Heart J* 66:572 1963
 17. Creck D I, Khouri I M and Kayford C K. Systemic and coronary energetics in the resting unanesthetized dog. *Circ Res* 16:107 1965
 18. Hood W B Jr, Johnson J, Kumar I, Katayama I, Neuman R S and Norman J C. Experimental myocardial infarction. I. Production of left ventricular failure by gradual coronary occlusion in intact conscious dogs. *Circulation* 43:773 1970
 19. Anderson I W. An introduction to multivariate statistical analysis. New York 1958. John Wiley and Sons Inc.
 20. Milnow M K. An electrocardiographic study of *Macaca mulatta*. *Behav Monit* 4:51 1966
 21. Hunkeler A I. Report of the deaths occurring in the Society's gardens during the year 1944. *Proc Zool Soc Lond* 117:371 1945
 22. Manning G W. Coronary disease in the dog. *Am Heart J* 23:719 1947
 23. Burlingame I. Annual report of the research and hospital department. *Zoonoses Res* 18:1 1915
 24. Ratchiff H I. Report of Penrose Laboratory. *Zool Soc Philadelphia* p 13 1961
 25. Ratchiff H I. Report of Penrose Laboratory. *Zool Soc Philadelphia* p 19 1967
 26. Ratchiff H I, Verasimides T C and Ellis C A. Changes in the character and location of arterial lesions in mammals and birds in the Philadelphia Zoological Garden. *Circulation* 21:730 1960
 27. Taylor C B, Patton D I and Cox C E. Atherosclerosis in rhesus monkeys. VI. Fat myocardial infarction in a monkey fed fat and cholesterol. *Arch Pathol* 76:404 1963
 28. Andrus S B, Fortman O W and Ruppel A J. Comparative studies of spontaneous experimental atherosclerosis in primates. I. Lesions in chimpanzees including myocardial infarction and cerebral aneurysm. *Progress in biochemical pharmacology*, vol 4. Basel and New York 1968. S. Karger AG, p 393
 29. Vinberg A, Mahanti B and Litvak J. Experimental gradual coronary artery constriction by Ameroid constrictors. *Surgery* 47:765 1960
 30. Nish C B, Davis I and Woodbury R A. Cardiovascular effects of anesthetic doses of pentobarbital sodium. *Am J Physiol* 180:101 1956
 31. Lee C N and Manning J W. Effect of sodium pentobarbital on electrical and reflex activation of the cardiovascular system. *Circ Res* 14:278 1964
 32. Ngai S H and Holme I. Effects of anesthetic doses on circulatory regulatory mechanisms in the dog. *J Pharmacol Exp Ther* 163:495 1966
 33. Blumgart H I and Zoll P M. Pathological physiology of aortic pectoris and acute myocardial infarction. *Circulation* 22:301 1960
 34. de Warrat A, Storm C J and Houman A K. J. Ligation of the coronary arteries in Japanese monkeys. II. Arrhythmias and conduction disturbances. *Am Heart J* 17:10 1936
 35. Forsyth K I and Bureuther K. Systemic arterial blood pressure and pulse rate in chronically restrained rhesus monkeys. *Am J Physiol* 212:1461 1967
 36. Agre C M. Management of coronary shock. *Am J Cardiol* 1:231 1958
 37. Erickberg C K. Cardiogenic shock in acute myocardial infarction. *Circulation* 23:325 1961
 38. Agre C M. Pathogenesis and management of coronary shock. *Circulation* 21:194 1966
 39. Lefkowitz M G and Harrison D C. Cardiogenic shock. A review. *Clin Pharmacol Ther* 10:119 1969

Friedreich's ataxia associated with idiopathic hypertrophic subaortic stenosis

David G. Ruschhaupt MD

Otto G. Thilenius MD PhD

Donald E. Cassels MD

Chicago Ill

Friedreich's ataxia (FA) is a progressive neurologic disorder frequently familial and most often beginning in childhood. In its classical form the disorder is characterized by spinal and cerebellar ataxia, diminution of the deep tendon reflexes, presence of extensor plantar responses, and the loss of appreciation for senses of vibration and touch. Optic atrophy is often present. Nonobstructive myocardial disease accompanying or may even precede the neurologic symptoms of this disorder.^{1,10}

In idiopathic hypertrophic subaortic stenosis (IHSS) restriction in left ventricular filling and obstruction to left ventricular outflow are the main hemodynamic disturbances.¹¹⁻¹³ Its etiology is as obscure as the etiology of Friedreich's ataxia. The electrocardiographic abnormalities in this disease may be identical to those seen in Friedreich's ataxia, including arrhythmias, voltage evidence for left ventricular hypertrophy, and T wave changes.

Association of these two disorders has not been described, and the probability of their unrelated occurrence in the same patient is exceedingly small. We would like to

present a patient with both these diseases; furthermore, we wish to report hemodynamic data of five additional patients with Friedreich's ataxia specifically studied for the presence of left and/or right ventricular outflow tract obstruction.

Case report

D. C., a Caucasian male patient, was born March 23, 1951. There was no family history of neurologic or cardiovascular diseases. The patient was first evaluated at the age of 10 years because he tired easily. There was no history of streptococcal infection or joint symptom. Routine neurologic examination was normal except that his gait was thought to be awkward. He did not show signs of congestive heart failure, and his peripheral pulses were normal. By palpation he had a slightly increased left ventricular impulse. The heart sound were within normal limits. A Grade 2/6 apical pinnate systolic murmur with radiation to the axilla was heard. The chest X-ray was normal. The electrocardiogram (ECG) demonstrated borderline left ventricular hypertrophy and negative T waves in Leads I, 2, aVR, and V₄ to V₆ (Fig. 1). The diagnosis of IHSS was suspected. Cardiac catheterization was performed at age 17 years (Table 1). Arterial and venous blood oxygen content was normal. Pressures across the right heart were within normal limits. At rest a 60 mm Hg systolic pressure gradient between the left ventricle and body (with a transseptal cath-

This case report is from the Department of Pediatrics, University of Chicago, Chicago, Ill.
Received for publication July 11, 1972; accepted for publication July 11, 1972.
Revised manuscript received July 11, 1972.
Reprint requests to Dr. Otto G. Thilenius, MD, 950 East 59th Street, Chicago, Ill. 60637.

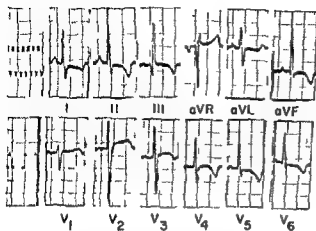


Fig. 1 Patient D C ECG demonstrating left ventricular hypertrophy and inverted T waves in Leads I II aVR and V₁ to V₄ (Patient is not taking any medication)

ter with 8 side holes and end hole) and the femoral artery (using a Courmand 18 G needle) existed only during postoperative ventricular contractions. Isuprel was infused at a rate up to 15 μ g per minute the left ventricular systolic pressure increased from 100 to 235 mm Hg (Fig 2) while femoral arterial systolic pressure fell from 100 to 85 mm Hg. The left ventricular angiogram showed marked hypertrophy of the ventricular wall and moderate muscular subvalvular obstruction. During the following two years this patient complained of increasing tiredness. At the age of 14 he underwent cardiac surgery. At the time of thoracotomy, cardiac enlargement was noted and was thought to be primarily due to an increase in muscle mass of the left ventricular wall. A systolic pressure gradient could again be demonstrated only during postoperative ventricular contractions. An aortotomy was performed. A region of the left ventricular outflow tract approximately 5 to 6 cm below the aortic valve was narrowed by a hypertrophied group of anteriorly placed muscle bundles. Some of this muscle was removed but the major portion of the procedure consisted of enlarging the outflow trough by the dividing and spreading of these muscle bundles. Histologically this muscle had the appearance of hypertrophy: there was no fibrosis, edema, inflammation or increased glycogen content. Postoperatively the patient had two grand mal seizures. He required a respirator for 10 days. He left the hospital during the fourth postoperative week. At the time of his discharge his intelligence was normal. The neurologic examination demonstrated some right sided weakness, some ataxia of the upper extremities and absent deep tendon reflexes. These findings were initially thought to be compatible with basilar artery insufficiency incurred at the time of surgery. The diagnosis of Friedreich's ataxia was made subsequently when limb and truncal ataxia increased when his speech became slurred and when bilateral optic atrophy was noticed. In 1968 three years following surgery the patient demonstrated all the clinical findings of Friedreich's ataxia. At that time his left ventricle was still mildly enlarged. The heart sounds were

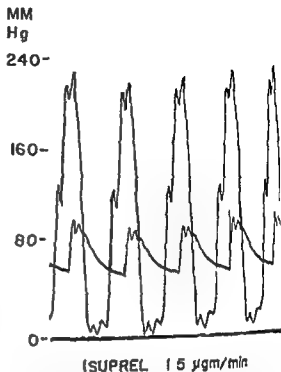


Fig. 2 Patient D C Tracing depicts simultaneous left ventricular and femoral arterial pressures during the infusion of Isuprel at a rate of 15 μ g per min. Note the notching of the ascending limb of the ventricular trace.

normal. There was a Grade 2/6 ejection systolic murmur heard along the upper left sternal border. There was no longer a separate apical murmur. The ECG continued to show borderline left ventricular hypertrophy and T wave inversion in Leads 2 aVR V₃ and V₄. Repeat cardiac catheterization (Table II) was normal neither during postoperative ventricular contractions nor during Isuprel infusion (up to 6 μ g per minute) nor during Valsalva maneuver and bicycle exercise was a pressure gradient present between the left ventricular body and the ascending aorta. Only the left ventricular end diastolic pressure rose during Isuprel infusion from 9 to 16 mm Hg. The cineangiogram demonstrated residual left ventricular hypertrophy but no obstruction of the outflow tract.

Methods of hemodynamic study of 5 patients with Friedreich's ataxia

Five patients of from 17 to 50 years of age with classical Friedreich's ataxia agreed to participate in a hemodynamic study of the possible relationship of this disease to HISS. Informed consent was obtained in each case. All of these patients had typical electrocardiographic T wave changes but normal left precordial voltages. Cardiac catheterization was performed under local anesthesia using two venous and two

1 m 34
h mbr 1

Table I Cardiac catheterization data of patient at age 12* with idiopathic hypertrophic subaortic stenosis and Friedreich's ataxia

	RA†	RI	PA	PC	LA	to	Heart rate (min)	Q (l/min)
Rest								
Phase	a = 10	76/9 ED	71/12	11	100/10 ED	100/60	95	4.1
Mean	6		18					
Postectopic ventricular contraction	—	—	—	—	110/15 FD	80/45	—	—
Isuprel 1.5 µg/min	—	—	—	—	230/15 ED	85/68	140	—

B 45.30 kg w ght 47.4 kg gram Ge val n shed a
 (Pr sure in mm Hg Abb e l ions RA = right at RI = right e tr I PA = pulmo ry t r P = s im nary cap il l m
 Q = m re Ad = see ding a ri LA = left at l Q = ca d t r B = body rfa e s ea ED = end-diastolic

Table II Cardiac catheterization data of patient at age 17* with idiopathic hypertrophic subaortic stenosis and Friedreich's ataxia

	RA†	RI	PA	PC	LA	to	Heart rate (min)	Q (l/min)
Rest								
Mean	6	27/6 FD	23/13	9	170/9 ED	170/85	90	5.5
Postectopic ventricular contraction	—	—	—	—	170/7 FD	120/85	—	—
Isuprel 6 µg/min	—	—	—	—	170/10 ED	175/80	160	—
5th min exercise (bicycle supine)	—	—	35/20	—	136/16 ED	135/90	150	10.7

BSA 1.69 m² w ght 58.3 kg gram Local ath a
 (Pr sure in mm Hg Abb e l ions RA = right at RI = right e tr I PA = pulmo ry t r P = s im nary cap il l m
 Q = m re Ad = see ding a ri LA = left at l Q = ca d t r B = body rfa e s ea ED = end-diastolic

arterial catheters to record simultaneously ascending aortic left ventricular pulmonary arterial and right ventricular pressures. The Fick method was used for estimation of cardiac output. An Isuprel infusion of up to 6 µg per minute was employed to enhance ventricular contraction. Fifteen minutes following Isuprel infusion a right ventricular biplane cineangiogram (frontal and lateral projection) and a single plane left ventricular cineangiogram (RAO projection) were made. Exercise studies were not undertaken because of the patient's inability to perform coordinated leg movement.

Case histories

Case 1 J. S. was born Jan. 30 1943. She has four normal siblings and no family history of Friedreich's

ataxia. Her early development was normal until age 10 when she began to have difficulty with her balance. At age 14 she could no longer walk unaided. Her understanding is normal but she has ataxic speech; her funds are normal. There is marked ataxia of trunk and extremities. She can type and feed herself but is restricted to a wheelchair. Proprioception is still present but markedly diminished. Deep tendon reflexes are absent. Plantar responses are extensor. She has pes cavus and some scoliosis of the spine. Physical examination of the cardiovascular system reveals slightly weak but symmetrical peripheral pulses. She has a normal apical impulse. S₁ is of normal intensity. S₂ is physiologically split. Murmurs cannot be heard. The ECG shows a normal sinus rhythm and an indeterminate axis; the precordial voltages are normal; the T waves are flat biphasic in Leads I, aVL, V₄ and V₆.

Case 2 L. D. was born Dec. 30 1937; she is the oldest of five children. One brother (Patient No. 3) has Friedreich's ataxia. By age 5 her gait was unsteady and her speech lurred. At age 15 she was confined to a wheelchair. At age 16 diabetes mellitus

ventricular wall thickness. Two patients (Cases 2 and 4) had an abnormally shaped left ventricular cavity. At end systole the left ventricular chamber was incompletely divided by prominent muscle ridges into a slitlike apical portion and a small conical subaortic portion. These same two patients also showed pronounced contractions of the right ventricular outflow tract without systolic pressure gradients. The angiogram of Case 3 showed a dilated left ventricular chamber with an apparently normal outflow tract, poor contractility and a larger than normal end systolic volume. Two patients (Cases 1 and 4) had distinctly dilated right coronary arteries. The patient with IHSS had dilatation of both right and left coronary arteries. None of the patients had angiographic evidence for narrowing of the coronary artery branches.

Discussion

The association of Friedreich's ataxia and idiopathic hypertrophic subaortic stenosis is highly intriguing. Both disorders have a familial incidence and affect the myocardium. Both become symptomatic approximately in the same age group. Electrocardiographic evidence for left ventricular hypertrophy and T wave abnormalities are common to both diseases. Yet the association of these disorders in one patient has not been reported.

Myocardial disease combined with degenerative disease of the central nervous system has been reported with certainty only in Friedreich's ataxia and in Refsum's disease.¹⁴ Friedreich¹⁵ himself described hypertrophy and fatty degeneration of the myocardium in some of his patients. Pitt⁴ emphasized the association of Friedreich's ataxia and heart failure. The onset of cardiac symptoms and their severity are extremely variable. Usually they develop long after the neurologic disorder is manifest; rarely does congestive heart failure precede the onset of neurologic signs.⁹ Palpitations and retrosternal chest pain have been the chief cardiac symptoms. As many as 90 per cent of the patients have electrocardiographic abnormalities which include atrial and ventricular arrhythmias and negative T waves in Leads I, II, III, and V₁ to V₂. Three of our patients had premature atrial contractions and all

patients had the typical I wave abnormalities. While left ventricular hypertrophy has been reported for almost half of the patients with Friedreich's ataxia, none of ours demonstrated abnormally tall R waves in the left precordial leads.

Hemodynamic studies done in patients with Friedreich's ataxia have demonstrated moderate degrees of ventricular dysfunction. The mean pulmonary capillary pressure and left ventricular end diastolic pressures have been reported as elevated (larger than 10 mm Hg) in patients with advanced neurologic disease.¹⁶ Two of these patients had selective cineangiograms which demonstrated pronounced contractions of the right ventricular outflow tract with a delayed wash out of contrast material. Muscular hypertrophy with dilatation of the left ventricle was also present. In another study¹⁷ a 34 mm Hg systolic pressure gradient across the left ventricular outflow tract was induced by Isuprel infusion. The angiogram of this case demonstrated dilatation and hypertrophy of the left ventricle.

In our study left ventricular hypertrophy was common to all patients. Two patients had abnormal degrees of left ventricular contractions at end systole; the left ventricular chamber appeared incompletely divided into a slitlike apical and a small conical outflow portion. However, significant pressure gradients were not present.

Diffuse myocardial hypertrophy is common to both IHSS and Friedreich's ataxia. In IHSS it involves chiefly the ventricular septum and the left ventricular outflow tract. The absence or presence of a pressure differential between left ventricular body and aorta depends on the functional behavior of the outflow tract. Increased ventricular wall thickness correlates with increased ventricular filling pressure noted in both diseases when an advanced stage is reached and it is then associated with a low cardiac output. Angiographically the ventricular end systolic volume may be small and ventricular contractions may appear to be forceful in both IHSS and Friedreich's ataxia. While a pressure gradient between the left ventricle and the aorta either at rest or during Isuprel infusion is as implied by the name part of

Table IV Hemodynamic data of 5 study patients with Friedrich's ataxia

Patient	Heart rate (min)	Cardiac index (L/min/M ²)	Stroke index (ml/M ²)	Rest				
				Pressures (mm Hg)				
				Pc	P1	RV	ao	LA
1 J S	70	2.9	42	—	22/6	27/4	110/75	110/10
2 L D	80	1.8	23	5	18/10	20/10	95/60	100/10
3 D D	85	3.0	35	11	24/10	24/8	110/85	110/10
4 J C	100	3.1	31	11	22/12	22/9	100/15	100/10
5 W C	90	2.5	28	7	26/8	26/4	140/80	140/10

Abbreviations: Pc = pulmonary capillary pressure; P1 = pulmonary artery; RV = right ventricle; ao = ascending aorta; LA = left ventricle.

IISS we have found it only in two out of six patients with Friedrich's ataxia. However, the obstructive component of IISS may not always be present and the restrictive component (restriction to ventricular filling) may be of even greater clinical significance.¹¹

It is apparent that there are distinct clinical and hemodynamic similarities in cardiomyopathy of Friedrich's ataxia and IISS and a comparison of the histological changes of these diseases is of interest. In Friedrich's ataxia the myocardium shows diffuse reticular fibrosis, the myocardial fibers are hypertrophied and also display degeneration with decreased cross striation and fatty metamorphosis.^{10,12} In some cases¹⁰ mononuclear cell infiltration and vacuolated and hyperchromatic nuclei have been seen. The coronary arteries may show all stages of intimal proliferation to the point of obstruction.^{10,12,13} In IISS myocardial hypertrophy and fibrosis are equally prominent findings; bundles of abnormally thick but short muscle fibers show a bizarre disordered arrangement and are separated by an increased amount of connective tissue, often with considerable fibrosis.²⁰ There may be extensive though focal degenerative changes with peripheral mononuclear cell infiltrates.²¹ Individual muscle fibers vary considerably in thickness and

show dystrophic changes and proliferation of sympathetic nervous fibers is evident.²² The coronary arteries have been reported to be dilated^{12,23} but are otherwise normal.¹ Tazze²⁰ noted repeatedly a smaller than normal number of branches coming from the left anterior descending coronary artery but was not certain whether this was an artifact (related to the method of injection with radiopaque material) or a real finding.

While the incidence of functional subaortic stenosis is higher in IISS and the degree of obstruction much more severe than in Friedrich's ataxia, the similarities in myocardial changes as well as in hemodynamics and clinical expression of heart disease are striking. A relationship of the respective etiological factors is a fascinating speculation.

Summary

Friedrich's ataxia and idiopathic hypertrophic subaortic stenosis (IISS) both diseases of unknown etiology, both result in hypertrophy and degenerative changes of the myocardium. Both diseases lead to nearly identical electrocardiographic changes. We report a patient who developed classical signs of Friedrich's ataxia several years after he was found to have moderately severe IISS. This observation

Isuprel infusion					Angiographic data
Rate mg/min	Pressures (mm Hg)				
	P1	P2	to	LI	
40	30/6	30/4	110/50	110/10	Increased left ventricular wall thickness Dilated right coronary artery
10	23/6	23/4	85/50	90/10	Increased left ventricular wall thickness Extreme systolic contraction
10	26/11	42/10	115/83	115/0	Increased left ventricular wall thickness
50	17/11	17/8	105/75	105/16	Increased left ventricular wall thickness Extreme systolic contractions Dilated right coronary artery
30	18/8	18/5	130/80	110/10	Increased left ventricular wall thickness Poor systolic contractions Moderate left atrial and left ventricular enlargement

prompted a hemodynamic study of five other patients with Friedreich's ataxia in search of a more common association and thus a possible etiological link between the two diseases. Cardiac catheterization was performed under local anesthesia. Catheters were inserted into the right ventricle, the pulmonary artery, the left ventricle and the aorta. Isuprel infusion up to 6 µg per minute was used in an attempt to induce an abnormal pressure gradient across the right or left ventricular outflow tract. Both right and left ventricular cineangiograms were obtained for evaluation of ventricular kinetics and wall thickness. Right and left heart pressures were normal at rest in all patients. During Isuprel infusion a 40 mm pressure gradient was induced across the left ventricular outflow tract in only one patient. A second patient developed a 16 mm gradient across the right ventricular outflow tract. All patients had low normal cardiac outputs. The angiograms demonstrated increased left ventricular wall thickness in all patients. It is concluded that systolic left and/or right ventricular outflow tract obstruction is only infrequently present in Friedreich's ataxia and is mild in degree. An etiological link between Friedreich's ataxia and HISS is not known at the present but may possibly exist and should be investigated.

Addendum

After this paper had been accepted for publication a first and single case report of hypertrophic obstructive cardiomyopathy associated with Friedreich's ataxia has appeared in the *American Journal of Cardiology* 27:436 1971.

The authors gratefully acknowledge the cooperation of Dr. Douglas N. Buchanan for allowing them to study his patients with Friedreich's ataxia. The authors are also grateful to Dr. George Dascoff who performed the surgery on patient D.C. and to Dr. Klaus Rammner who kindly provided radiological consultation.

REFERENCES

- Boyer S. H. IV, Chisholm A. W. and McKusick V. A. Cardiac aspects of Friedreich's ataxia. *Circulation* 20:493 1967.
- Friedreich N. Über degenerative Atrophie der linken Hinterhirn. *Arch. Path. Anat.* 26:391 and 433 1863.
- Hewer R. L. The heart in Friedreich's ataxia. *Brit. Heart J.* 31:5 1969.
- James T. N. and Fisch C. Observations on the cardiovascular involvement in Friedreich's ataxia. *AMER. HEART J.* 66:164 1963.
- Lorenz T. H., Kurtz C. M. and Shapiro H. H. Cardiopathy in Friedreich's ataxia. *Arch. Intern. Med.* 86:412 1950.
- Mann C. W. Cardiac manifestation in Friedreich's ataxia. *AMER. HEART J.* 39:799 1950.
- Nada A. S., Ahmanson M. M. and Sieracki L. A. Cardiac manifestations of Friedreich's ataxia. *New Eng. J. Med.* 241:732 1951.

- 8 Pitt N On a case of Friedreich's disease
Guy Hosp Rep 44:369 1887
- 9 Thilenius O G and Groisman B J Friedreich's ataxia with heart disease in children
Pediatrics 27:246 1961
- 10 Thorén C Cardiomyopathy in Friedreich's ataxia
Acta Paediatr Scand 53:Suppl 153 1964
- 11 Braunwald E Brockenbrough E C and Morrow A G Hypertrophic subaortic stenosis
Circulation 26:161 1962
- 12 Braunwald F Lambrew C T Rockoff S D Ross J Jr and Morrow A G Idiopathic hypertrophic subaortic stenosis
Circulation 30:141 1964
- 13 Frank S and Braunwald E Idiopathic hypertrophic subaortic stenosis
Circulation 37:759 1968
- 14 Goodwin J F Congestive and hypertrophic cardiomyopathies
Lancet 1:731 1970
- 15 Wolstenholme G E W and O'Connor M editors Cardiomyopathies Boston 1964 Little Brown & Co
- 16 Gordon N and Hudson R F B Refsum's syndrome Hereditary ataxia polyneuropathy
Brain 82:41 1959
- 17 Moore A A D and Lambert E C Cardiomyopathy associated with muscular and neuromuscular disease in Watson H editor
Pediatric cardiology St Louis 1963 The C V Mosby Company
- 18 Ivarmark B and Thorén C The pathology of the heart in Friedreich's ataxia
Acta Med Scand 175:227 1964
- 19 Russell D S Myocarditis in Friedreich's ataxia
J Path Bact 58:739 1946
- 20 Teare R D The pathological recognition of obstructive cardiomyopathy in Wolstenholme G E W and O'Connor M editors
Cardiomyopathies Boston 1964 Little Brown & Co
- 21 Lannigan R Hypertrophic subaortic stenosis with myocardial fibre degeneration
Brit Heart J 27:772 1965
- 22 Leane A G F The histochemistry and electron microscopy of obstructive cardiomyopathy in Wolstenholme G E W and O'Connor M editors
Cardiomyopathies Boston 1964 Little Brown & Co
- 23 Steiner R F Radiology of hypertrophic obstructive cardiomyopathy in Wolstenholme G E W and O'Connor M editors
Cardiomyopathies Boston 1964 Little Brown & Co

Congenital pulmonary and subclavian arteries steal syndrome

Keda M. Shaher, MD

Paul Patterson, MD

Allan Stranahan, MD

Thomas O'der, MD

Matthew Firma, MD

Monica Bishop, MD

Albany, N. Y.

Cerebrovascular insufficiency produced as a result of reversal of blood flow in the vertebral artery secondary to occlusion in the proximal subclavian or innominate arteries is referred to in the literature as the subclavian steal syndrome.^{1,2} In the majority of cases the central nervous system symptoms are secondary to acquired retrograde flow in the vertebral artery. Congenital subclavian artery steal syndrome has been described secondary to stenosis or atresia of the intrathoracic portion of the subclavian artery.^{3,4} Acquired subclavian steal has been noticed after the Blalock-Taussig operation.⁵ Recently, an infant was seen at Albany Medical Center Hospital with central nervous system symptoms and a pansystolic murmur to the left of the sternum. Cardiac catheterization and angiography demonstrated retrograde blood flow in the left vertebral and left common carotid arteries secondary to anomalous communication between these

two vessels and the pulmonary artery. The object of this paper is to report this interesting case.

Case report

T.R., a 7-month-old infant, had been admitted to Albany Medical Center Hospital at the age of 2 days for multiple congenital anomalies. The mother had had a severe infection in the upper respiratory tract during the fifth month of her pregnancy. Delivery was at term and uneventful and the birth weight was 3 pounds and 5 ounces. Amniotic fluid was reportedly excessive and low set ears, perihemeral palsy of the right side of the face and choanal atresia were noted at birth. The family history revealed that the parents were both 27 years old. Two other siblings, ages 5 and 4 years, were alive and well. On physical examination the infant was small and abnormal looking and had a head circumference of 35.5 cm, which was at the fifth percentile. The anterior fontanel was open and soft and the sutures were overriding. The patient was unable to close the right eyelid and was unable to move the right side of the mouth. The right ear was grossly deformed. There was apparent choanal atresia in the right nostril with thick white secretions. The mandible was small and the infant had a

From the Department of Pediatrics and Pathology, Albany Medical College, Albany, N. Y.

Received for publication July 15, 1977.

Reprint requests to Dr. Keda M. Shaher, Head of Pediatrics, Albany Medical College, 1111 Central Avenue, Albany, N. Y. 12208.

- 8 Pitt N On a case of Friedreich's disease
Guy Hosp Rep 44 369 1887
- 9 Thilenius O G and Grossman B J Fried-
reich's ataxia with heart disease in children
Pediatrics 27 246 1961
- 10 Thorén C Cardiomyopathy in Friedreich's
ataxia Acta Paediat Scand 53 Suppl 153
1964
- 11 Braunwald E Brockenbrough E C and
Morrow A G Hypertrophic subaortic ste-
nosis Circulation 26 161 1962
- 12 Braunwald F Imbrow C T Lockoff
S D Ross J Jr and Morrow A G Idi-
opathic hypertrophic subaortic stenosis
Circulation 30 IV 1 1964
- 13 Frank S and Braunwald E Idiopathic hyper-
trophic subaortic stenosis Circulation 37 759
1968
- 14 Goodwin J F Congestive and hypertrophic
cardiomyopathies Lancet 1 731 1970
- 15 Wolstenholme G F W and O'Connor M
editors Cardiomyopathies Boston 1964 Little
Brown & Co
- 16 Gordon N and Hudson R F H Refsum's
syndrome Hereditary ataxia polyneuritis
formis Brain 82 41 1959
- 17 Moore A A D and Lambert E C Cardio-
myopathy associated with muscular and neuro-
muscular disease in Watson H editor
Paediatric cardiology St Louis 1968 The
C V Mosby Company
- 18 Ivarmark H and Thorén C The pathology
of the heart in Friedreich's ataxia Acta Med
Scand 175 227 1964
- 19 Russell D S Myocarditis in Friedreich's
ataxia J Path Bact 58 739 1946
- 20 Teare R D The pathological recognition of
obstructive cardiomyopathy in Wolstenholme
G F W and O'Connor M editors Cardio-
myopathies Boston 1964 Little Brown & Co
- 21 Lannigan R Hypertrophic subaortic steno-
sis with myocardial fibre degeneration Brit Heart
J 27 772 1965
- 22 Pearce A G E The histochemistry and elec-
tron microscopy of obstructive cardiomyopathy
in Wolstenholme G F W and O'Connor M
editors Cardiomyopathies Boston 1964 Little
Brown & Co
- 23 Steiner R E Radiology of hypertrophic ob-
structive cardiomyopathy in Wolstenholme
G F W and O'Connor M editors Cardio-
myopathies Boston 1964 Little Brown & Co

10 of 51
 \ mbe 1

(Fig. 4) The left side of the heart was entered from the right atrium through an atrial septal defect. The ascending aorta arose from the left ventricle and formed a right sided aortic arch and thoracic aorta. The aortic arch gave origin to two branches—the right common carotid and the right subclavian arteries. There was no apparent connection between the ascending aorta or the right aortic arch and the vessel to the left of the spine that gave origin to the left common carotid and the left subclavian arteries (Fig. 5). A small vessel however connected the right thoracic aorta to the pulmonary artery. Selective injection of dye into the left ventricle and right aortic arch opacified the right common carotid and right vertebral arteries and the ipsilateral cerebral vessels. A few seconds later the left common carotid and the left subclavian arteries were seen to opacify retrogradely from the cerebral circulation. From these two vessels the large vessel to the left of the spine and the pulmonary artery opacified (Fig. 6).

After cardiac catheterization the patient underwent thoracotomy for a possible vascular ring. The small vessel which connected the right thoracic aorta to the main pulmonary artery was identified as a small right patent ductus arteriosus and was divided. The large vessel which arose from the pulmonary artery and gave origin to the left common carotid and left subclavian arteries was identified as the left dorsal (thoracic) aorta. Since the blood flow in this vessel was in a retrograde fashion the vessel was ligated at its junction with the pulmonary artery. The child died after the operation was completed.

At autopsy the left cerebral hemisphere was slightly smaller than the right hemisphere. Similarly the vertebral artery on the left was smaller than the one on the right. There was a Meckel's diverticulum 34 cm. proximal to the cecum and it measured 1.3 cm. Microscopically it showed gastric mucosa in one region. The heart was slightly enlarged and weighed 130 gm. The great arteries were normally situated but the pulmonary artery appeared to be slightly larger than the aorta. The aortic arch and thoracic aorta were situated on the right side (Fig. 7). The aortic arch gave origin to the right common carotid and the right subclavian arteries. The pulmonary artery gave rise to four branches—the right and left pulmonary arteries, the left dorsal (thoracic) aorta and a small right patent ductus arteriosus. The latter two vessels had been ligated surgically at their origin from the pulmonary artery. Superiorly the left dorsal (thoracic) aorta divided into the left common carotid and the left subclavian arteries. The right ductus arteriosus connected the pulmonary artery to the junction between the right aortic arch and the right thoracic aorta. There was an ostium secundum atrial septal defect that measured 5 by 5 mm. The systemic and pulmonary veins and the coronary arteries were normal.

Discussion

The primary embryonic arteries are the right and left primitive aortae. According to Hamilton, Boyd and Mossman⁸ each primitive aorta can be readily divided into three portions: (1) a short ventral ascending



Fig. 1. Chest x-ray film at 2 days of age shows no cardiac enlargement and normal pulmonary vascularity. The aortic arch is probably situated on the right side.

Table I. Cardiac catheterization

Site	Oxygen saturation (%)	Pressure (mm Hg)
Superior vena cava	46	
Inferior vena cava	63	
Right atrium	60	2
Right ventricle	—	35/0
Pulmonary artery	74	35/10
Left atrium	94	2
Left ventricle	92	80/10
Left dorsal aorta	93	40/35

portion (2) a primitive (first) aortic or pharyngeal arch artery and (3) a relatively long descending portion which distributes the blood from the heart to the embryonic tissues. When the process of fusion of the endothelial cardiac tube reaches the anterior limit of the pericardial cavity it extends forward to involve the cardiac extremities of the two ventral aortae. As a result the bulbous cordis is continuous cranially beyond the pericardium with a single midline vessel called the truncus arteriosus or aortic sac. The right and left first aortic arch arteries arise from this vessel. With the formation of further pharyngeal arches the first pair of aortic arch arteries is supplemented by the successive addition of five more pairs, one in each of the arches. The dorsal aortae fuse toward their caudal extremities to form a

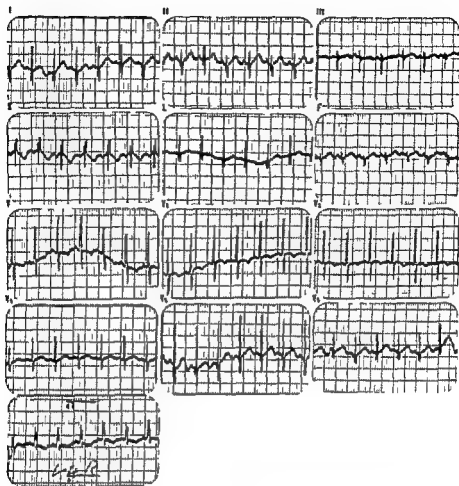


Fig 1 Electrocardiogram at 2 days of age shows left axis deviation

poor suck and a poor cry. The tongue and pharynx appeared to be normal. Examination of the lungs revealed coarse rhonchi throughout. Examination of the cardiovascular system revealed a markedly diminished left brachial pulse and almost no left carotid pulse. On auscultation of the heart, the second sound was single and a soft ejection murmur was heard in the pulmonary area. There was no evidence of hepatosplenomegaly. Examination of the extremities revealed digitalization of the thumb and the fourth and fifth digits were noted to overlap. There was a wide space between the first and second toes. The electrocardiograph showed a left axis deviation but there was no evidence of abnormal ventricular hypertrophy (Fig 1). The chest x-ray film suggested a right aortic arch (Fig 2). The urine analysis was within normal limits and the electrolytes, glucose and blood urea nitrogen were normal. The hemoglobin was 14.6 Gm, hematocrit 47 and white blood count 7,000. The cerebrospinal fluid was clear and not under tension. The sugar was 66 mg, protein 87 mg, and cell count 1,000 fresh and crenated red blood cells. No white cells were seen. Cultures were negative. Skeletal examination of both hands demonstrated no bony architectural abnormalities. Since the infant was unable to swallow, he was fed by tube. Chromosome studies revealed no anomalies detectable in the peripheral smear. Laboratory tests ruled out toxoplasmosis, rubella, and cytomegalia inclu-

sion disease. Urinary and serum amino acids were also normal.

The patient remained in the hospital, was fed by tube, and was given antibiotics from time to time because of recurrent chest infections. When he was 2 months old, the cardiovascular system was reassessed and a Grade 2/4 continuous murmur was noted beneath the left clavicle. In addition, the left subclavian and carotid pulses were impalpable. The electrocardiogram showed deep Q waves in Lead V₄, suggesting left ventricular hypertrophy (Fig 3). The chest x-ray film showed increased pulmonary vascularity. Since the combination of a continuous murmur and a lack of left subclavian and left carotid pulses suggested a vascular abnormality and possibly a vascular ring, cardiac catheterization was performed through the right femoral vein on Sept 17, 1968. The pressures and samples are shown in Table 1. The pressures in the right ventricle and pulmonary artery were slightly elevated. A left-to-right shunt was observed at the atrial and pulmonary arterial levels. While in the pulmonary artery, the catheter intubated a vessel to the left of the vertebral column. The pressure in this vessel was equal to that in the pulmonary artery, but the blood in it was 93 per cent saturated with oxygen. Superiorly, this vessel bifurcated and gave origin to the left subclavian and the left common carotid arteries. Inferiorly, the vessel terminated in the main pulmonary artery.

J. L. Mc 84
V. mb 1

single midline vessel lying between the developing gut ventrally and the notochord dorsally. The first pharyngeal arch arteries disappear at about the time that the third arch arteries are fully differentiated. Involution of the second arch arteries follows as the fourth arch arteries mature and increase in size. The fifth pair is never well developed and its arteries are present for only a very short time. At the end of the somitic period the sixth arch arteries give off descending branches to the plexuses of the lung buds and are called pulmonary arches. Later during the course of development the truncus arteriosus is divided by the spiral septum in such a way that the blood from the right ventricle comes to empty into the sixth arches while that from the left ventricle is distributed to the third and fourth arteries. At a later stage of development the segment of the dorsal aorta between the third and fourth arches on each side disappears. At the same time the segment of the right dorsal aorta between the right fourth arch artery and its junction with the left dorsal aorta and the lateral portion of the right sixth arch artery disappear. Blood from the heart can now pass to the single descending aorta only by way of the left fourth and sixth arch arteries. The terminal part of the latter persists as the ductus arteriosus until full term. The aortic sac is left horn and the left fourth arch artery form the arch of the definitive aorta. The right horn of the aortic sac elongates to become the innominate artery which terminates by giving origin to the right third and fourth arch arteries. The former of these branches becomes the right common carotid artery and the commencement of the right internal carotid artery. The right fourth arch artery forms the stem of origin of the right subclavian artery. The left subclavian artery arises by the hypertrophy of a segmental branch of the left dorsal aorta.

It would seem therefore that the embryological explanations of the congenital vessel anomalies of our patient could be as follows. The right and left dorsal aortae have persisted. The point of communication between the left dorsal aorta and the pulmonary artery must represent a left patent ductus was the only way a systemic artery can communicate with the pulmonary artery

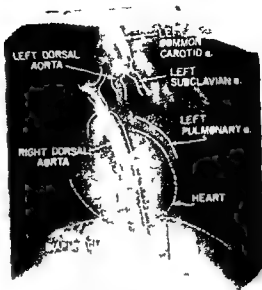


Fig. 6 An aortic root angiogram. This frame was taken a few seconds after that shown in Fig. 5. Notice retrograde filling of the left common carotid and left subclavian arteries. These two vessels feed the brain artery which arose from the pulmonary artery.

is through a patent ductus. Our patient therefore had a right and a left patent ductus arteriosus. Disappearance of the segment of the left thoracic aorta beyond the left sixth arch would account for the presence of a right descending aorta. The right aortic arch must have developed from the right fourth arch artery and the right common carotid artery from the right third arch artery. The right subclavian artery must have developed from a segmental branch of the right dorsal aorta. Since there was no communication at any level between the two thoracic aortae the left fourth arch artery probably had not developed at all and the left subclavian artery must have developed from hypertrophy of a segmental branch of the left thoracic aorta.

Clinical evaluation of the central nervous system of the patient during life demonstrated a right peripheral nerve palsy and dysphagia. In all probability these two conditions were not related to the vascular problem. The facial palsy was probably traumatic and the dysphagia secondary to choanal atresia. As pointed out by other workers^{4,7} central nervous system signs are uncommon in the congenital variety of the

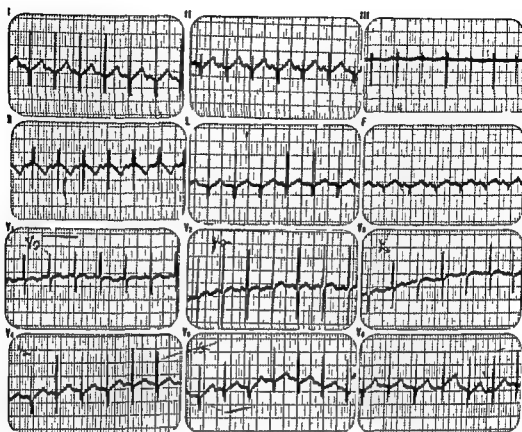


Fig 3 Electrocardiogram at 2 months of age shows left axis deviation and deep Q waves in lead V4

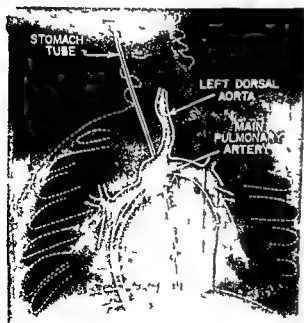


Fig 4 A pulmonary arterial angiogram shows a large vessel that originated from the pulmonary artery to the left of the spine

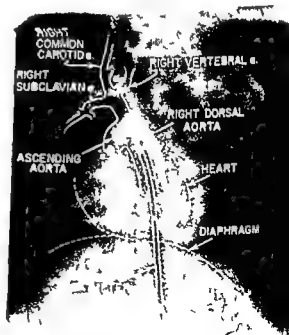


Fig 5 An aortic root angiogram shows right aortic arch and right thoracic aorta. Note opacification of the right subclavian, right common carotid and right vertebral arteries

Summary

A 2 month old infant was seen at Albany Medical Center Hospital with right peripheral facial palsy and dysphagia. Evaluation of the cardiovascular system showed a lack of left common carotid and left subclavian pulses. A continuous murmur was heard to the left of the sternum. Cardiac catheterization and angiography demonstrated retrograde filling of the left common carotid artery, the left subclavian artery, a left dorsal aorta and the pulmonary artery from the opposite side of the cerebral hemisphere. Autopsy revealed a right aortic arch and a right thoracic aorta. The right common carotid and right subclavian arteries arose from the right aortic arch. A large left dorsal aorta arose from the pulmonary artery and divided superiorly into the left common carotid and the left subclavian arteries. There was no communication between the two aortae. The central nervous system signs were thought not to be secondary to pulmonary artery steal. It was suggested that a lack of pulses and a continuous murmur would suggest such a diagnosis.

REFERENCES

- 1 Fisher C M Editorial New Eng J Med 266:818 1961
- 2 Revick M, Holling H E, Roberts B and Toole J F Reversal of blood flow through the vertebral artery and its effect on cerebral circulation New Eng J Med 266:878 1961
- 3 Piccone V A Jr and Leveen H H The subclavian steal syndrome Ann Thorac Surg 9:31 1970
- 4 Massumi R A The congenital variety of the subclavian steal syndrome Circulation 28:1149 1963
- 5 Bradley W G Congenital aortic arch abnormalities with the subclavian steal pattern of blood flow Brit Heart J 28:718 1966
- 6 Antia A V and Ottesen O E Collateral circulation in subclavian stenosis or atresia. Angiographic demonstration of retrograde vertebral subclavian flow in two cases with right aortic arch Amer J Cardiol 18:599 1966
- 7 Gerber N Congenital atresia of the subclavian artery producing the subclavian steal syndrome Amer J Dis Child 113:709 1967
- 8 Folmer G M and Shah K D Subclavian steal in patients with Blalock-Taussig anastomosis Circulation 31:741 1965
- 9 Hamilton W J, Boyd J D and Mossman H W Human embryology ed 3 Cambridge 1967 W Heffer & Sons Ltd

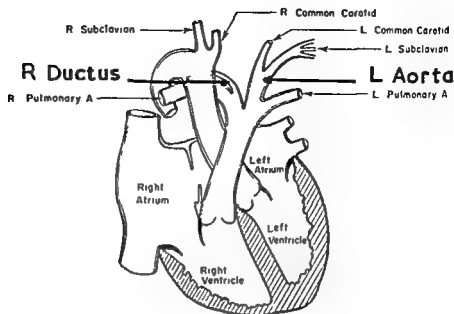


Fig. 7 Diagrammatic illustration of the cardiac findings at autopsy

subclavian artery steal. In this context, we have to emphasize that, in the congenital variety of this syndrome, the steal is from the basilar system. In our patient the steal was from both the basilar system and the circle of Willis.

Although cardiac catheterization and selective angiocardiography demonstrated that the left common carotid artery, left subclavian artery, and left dorsal aorta were being fed by blood from the opposite cerebral hemisphere, the pathophysiology of this congenital abnormality did not become clear to us until after surgery and autopsy. The shunt at the pulmonary arterial level had been interpreted as a patent ductus arteriosus but we could not explain the low pressure in the left thoracic aorta and its two branches. A vascular ring was thought to be the most plausible explanation. Undoubtedly the fact that this condition has not been described before explains the difficulties we have had in making the diagnosis during life.

The various conditions which can give rise to a continuous murmur to the left of the sternum are well recognized. To the best of our knowledge, a continuous murmur caused by pulmonary artery steal has never been described before. The etiology of this murmur in our patient was probably the continuous flow of blood from the left dorsal aorta to the pulmonary artery

throughout the two phases of the cardiac cycle. Blood flow through the right ductus must have also contributed to this murmur.

We believe that "pulmonary and subclavian arteries steal syndrome" should be suspected when there is a continuous murmur to the left of the sternum and a lack of carotid and brachial pulses. Only cardiac catheterization will demonstrate a left to right shunt at the pulmonary arterial level and low pressure in the common carotid and subclavian arteries. Angiography of the opposite carotid artery should establish the diagnosis since it will demonstrate retrograde blood flow in the carotid and vertebral arteries of the affected side. Moreover delayed opacification of the pulmonary artery should be observed. We believe that the anatomic anomalies described here are probably extremely rare. On the other hand the basic physiologic concept of the pulmonary and subclavian arteries steal should not be all that rare and probably various combinations of anomalies of the aortic arches would give rise to the same clinical picture. It is suggested therefore, that this condition should be suspected in any patient who has unilateral absence of the carotid and subclavian pulses and a continuous murmur. Surgical ligation of the pulmonary end of the anomalous vessel and anastomosis of its distal end to the aorta should correct the hemodynamic abnormalities

V. m. 84
V. m. 1



Fig. 1 Thoracic roentgenogram

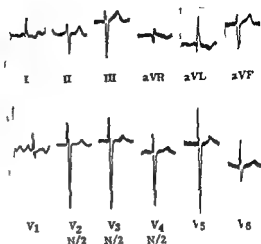


Fig. 2 ECG

restriction of salt intake and administration of diuretics and digitalis.

At the age of 20 years the patient was admitted for further study so as to determine whether further surgical intervention was possible and advisable. A moderate degree of congestive cardiac failure was recognized. The hemoglobin was 16.5 Gm. per 100 ml. of blood. Since this was considered a relatively low level for a cyanotic patient she was treated with oral iron replacement with a subsequent rise in the hemoglobin level to 21.5 Gm. per 100 ml. of blood. This in turn was associated with improvement in her clinical condition although signs of congestive failure remained. The physical findings remained unchanged with the patient showing marked cyanosis.

DR ROBERT A. VAN TASSEL Perhaps Dr Amplatz will show the x rays.

DR KURT AMPLATZ This is a roentgenogram taken when the patient was 20 years old (Fig. 1). The cardiac silhouette is grossly enlarged with biventricular prominence. There is pectus carinatum. The left hemidiaphragm is elevated. In the left pleura there are prominent signs of effusion and/or pleural thickening, with pleural effusion being the most likely possibility. The pulmonary vascularity is normal and there is no evidence of a left to right shunt. Scoliosis is very evident.

DR VAN TASSEL Thank you Dr Amplatz. Dr Moller would you care to look at the electrocardiogram (ECG) (Fig. 2) from the patient's last admission and interpret it for us?

DR JAMES H. MOLLER The rhythm is that of atrial fibrillation with occasional premature ventricular contractions. Left axis

deviation associated with a counterclockwise rotation of the QRS loop in the frontal plane is present. There is no specific pattern of ventricular hypertrophy although the major forces are posteriorly directed. ST and T wave changes are present.

DR VAN TASSEL I shall continue with the admission when the patient was 20 years old. A spleen and liver scan was normal. Studies revealed a large right-sided Blalock-Taussig anastomosis. The pressure in the ascending aorta was 100/60 mm Hg.

From the aorta the catheter was advanced into the right pulmonary artery through the Blalock-Taussig anastomosis. The pressure in the right pulmonary artery was found to be 80/50 mm Hg and the mean pressure 60 mm Hg. No further operation was advised.

Two months after the final admission and while in a state of congestive cardiac failure the patient died in her home community.

Dr Moller will you discuss the differential diagnosis?

DR MOLLER This young adult who died at the age of 20 years showed cyanosis in the neonatal period which then persisted throughout her life. One of the most prevalent causes of cyanosis in the neonatal period is complete transposition of the great vessels. The majority of patients with this condition die within the first few months of life. The persistence of cyanosis however over a long period of time starting from the neonatal period is most commonly

Clinical pathologic conference

Robert I. Van Lassel, MD
Kurt Amplatz, MD
James H. Moller, MD
Franklin H. Martin, MD
Jesse I. Edwards, MD
St. Paul, Minn.

Case report

DR ROBERT I. VAN LASSEL: A female child when born to a diabetic mother after 36 weeks gestation weighed 8 pound 13 ounce. Cyanosis was noted at birth and persisted throughout her life. Both growth and development were retarded. At the age of 18 months, cardiac catheterization was performed and although the results were inconclusive a tentative diagnosis of pulmonary arteriovenous malformation. Complaints of dyspnea on exertion and fatigue were first elicited when she began school. The results of a second cardiac catheterization performed at the age of 8 years again were inconclusive but suggested pulmonary arteriovenous. At this study however it was established that there was continuity of the inferior vena cava with theazygos vein and connection of a left superior vena cava with the left atrium. Following this catheterization procedure the patient developed thrombophlebitis in the right leg which was used for the study and she experienced an episode diagnosed as pulmonary embolism. Although she recovered from this episode permanent swelling of the right leg remained. At the age of 9 years for reasons not clear in the record digitalis and a diuretic therapy were initiated.

At the age of 14 years the patient was referred to the University of Minnesota Hospitals for further cardiac evaluation because of an increasing degree of cyanosis. Additional history revealed increasing dyspnea decreasing exercise tolerance, the onset of dizzy spells and substernal chest pain which occurred with exercise. Physical examination revealed a small frail cyanotic female child. She was 58 inches tall and weighed 38.2 kilograms. The blood pressure was 126/10 mm Hg, and the pulse was 68 beats per minute and irregular. The femoral pulses

were normal. Both the finger and the toes revealed prominent clubbing. Marked scoliosis of the thorico-lumbar spine was noted and associated with marked thoracic deformity. The lungs were clear and the precordium active. The point of maximal impulse was at the sixth intercostal space in the left anterior axillary line. A suprasternal thrill was present. The first cardiac sound was prominent and the second sound was single and of normal intensity. A Grade 2/6 systolic ejection murmur was present over the entire precordium but heard best below the left clavicle. A Grade 1/6 low pitched diastolic murmur was heard over most of the precordium. The splenic tip was palpable on deep inspiration but the liver was not considered to be enlarged. The right leg was markedly swollen and the superficial veins were distended. Minimal swelling in the left ankle was present.

Cardiac catheterization was performed during this admission also. This study identified the venous anomalies previously observed and also revealed signs of tetralogy of Fallot with pulmonary atresia. The pulmonary artery was neither visualized on angiography nor entered with the catheter during the procedure. One year later at the age of 15 years a Blalock-Taussig anastomosis was performed on the right side. At operation the surgeon noted the right pulmonary artery to be 12 mm wide and under low pressure. The right subclavian artery which was 5 mm in diameter was connected to the right pulmonary artery by an end-to-side anastomosis. The patient improved following operation she showed less cyanosis and improved exercise tolerance. Six weeks following the operation however the patient was noted to be in a state of congestive heart failure for which she was treated with

From the Department of Pathology, Charles T. Miller Hospital, St. Paul, Minn., and the Departments of Medical and Pediatric Radiology and Pathology, University of Minnesota, Minneapolis, Minn.
Supported by Public Health Service Research Grant 5 RO1 HL 05694 and Research Training Grant 5 TO1 HL 05570 from the National Heart Institute and by the Otto Bremer Foundation.
Received for publication May 28, 1971.
Reprint requests to Dr. Jesse I. Edwards, Charles T. Miller Hospital, 125 W. College Ave., St. Paul, Minn. 55102.

to development of pulmonary hypertension although it would not be severe since the child did not show a pattern of pulmonary edema.

In summary I think the child has the polysplenic syndrome with an endocardial cushion defect and tetralogy of Fallot. The lungs will show occlusive pulmonary vascular disease.

DR VAN TASSEL: Thank you Dr Moller. Dr Martin, would you please describe the necropsy findings?

DR FRANKLIN H. MARTIN: At necropsy the findings of major significance included both venous and cardiac anomalies.

There was thoracic kyphoscoliosis with the convexity of the spine directed toward the right. The mediastinal structures were shifted slightly toward the left. Each pleural cavity was obliterated by dense fibrous adhesions. Each lung possessed two lobes and the left lung was hypoplastic (Fig. 3). The heart was enlarged with its apex being midline in type. Major anomalies of the systemic veins were present.

Within the heart two complexes were present, namely the complete variety of persistent common atrioventricular canal (so called endocardial cushion defect) and the tetralogy of Fallot.

The former was characterized by (1) a large defect in the lowermost portion of the atrial septum; (2) clefts in the septal tricuspid and in the anterior mitral leaflets yielding a common atrioventricular valve; and (3) a defect of the ventricular septum leading to subvalvular interventricular communication (Fig. 4).

Above the atrial septal defect, which was part of the persistent common atrioventricular canal, the atrial septum showed an additional opening of about 1.0 cm in diameter. This opening was in the position of interatrial ostium II. No distinct fossa ovalis could be identified.

Although the right atrial appendage was somewhat larger than the left, each was characterized by being relatively long compared to the width. Muscular ridges were present in each but neither showed features characteristic of pectinate muscles. A small organized thrombus was present in the right appendage (Fig. 4a).

The lining of each ventricle, particularly

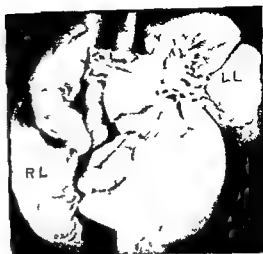


Fig. 3 Thoracic organs viewed from in front. The right lung (RL) is bilobed. This is the left lung (LL). The latter is hypoplastic. The apex of the heart is midline in type.

the left was unusually trabeculated (Fig. 4b). The outflow tract of the right ventricle was narrow by virtue of a vertical crista (Fig. 5a). The narrowed infundibulum led to the pulmonary valve. The latter was bicuspid, dome shaped and highly stenotic (Fig. 5b). Behind the vertical crista the aorta straddled the defective ventricular septum as it arose from both ventricles. Continuity existed between the aorta and the anterior leaflet of the common atrioventricular valve.

Of additional interest were the systemic veins (Fig. 6). The inferior vena cava was abnormal in its course and position. In the abdomen it lay to the left of the aorta (Fig. 6a).

Above the renal veins the inferior vena cava deviated toward the right but failed to pass through the liver. Instead it entered the right hemithorax to become continuous with the azygos vein. The latter, which was unusually wide, joined the right superior vena cava (Fig. 6b). The hepatic veins joined to form a common hepatic vein which in turn joined the right atrium where normally the inferior vena cava enters.

There were two superior vena cavae. The left, which received the hemiazygos vein, joined the left atrium directly (Fig. 6c) and the right entered the right atrium in the usual position. In the superior medi-

associated with tetralogy of Fallot or a condition closely related functionally such as single ventricle with pulmonary stenosis. Although unusual, there are a few instances of tricuspid atresia with cyanosis in the newborn period and survival of the patient for as long as 20 years. At cardiac catheterization this patient was found to have pseudotruncus arteriosus indicating the presence of an interventricular communication and maximum obstruction to pulmonary blood flow.

Two of the laboratory features which this patient presents, however, are unusual for typical pseudotruncus arteriosus. One is the electrocardiographic pattern of left axis deviation and counterclockwise rotation of the QRS loop in the frontal plane associated with small R waves over the right precordium. In many ways the ECG might fit better a diagnosis of tricuspid atresia with hypoplastic right ventricle than pseudotruncus arteriosus. In the latter condition the classical feature of elevated right ventricular systolic pressure would make one anticipate a pattern of right ventricular hypertrophy. Aside from tricuspid atresia, endocardial cushion defect (persistent common A-V canal) is the other common condition associated with left axis deviation. Virtually all patients with endocardial cushion defect present left axis deviation in the ECG. If this patient were to have an endocardial cushion defect with elevated right ventricular pressure, she should manifest right ventricular hypertrophy. Perhaps the precordial leads which lack a pattern of right ventricular hypertrophy indicate hypoplastic right ventricle.

Continuity of the inferior vena cava with the azygos vein is another unusual feature. This condition is commonly present in patients with the polysplenic syndrome. This syndrome is associated with fairly characteristic congenital cardiac malformations and other visceral anomalies. Many of these patients have an endocardial cushion defect. As a group, however, they do not manifest evidence for obstruction to pulmonary blood flow. I would think, however, in view of the continuity of the inferior vena cava with the azygos vein, the ECG and the clinical picture, that the intracardiac defect is of the endocardial

cushion type associated with the hemodynamics of the tetralogy of Fallot. Perhaps slightly supportive evidence for this view is the presence of atrial fibrillation in the ECG. This finding, to me, in congenital heart disease indicates a greatly enlarged atrium which one might anticipate in the face of an endocardial cushion defect. My clinical diagnosis is as follows: polysplenic syndrome with associated visceral anomalies, endocardial cushion defect, tetralogy of Fallot, and perhaps a small right ventricle.

I think the course of the child is unusual and deserves some clinical comment. The child underwent a Blalock-Taussig anastomosis which was of sufficient size as to lead to the development of cardiac failure. Subsequently, she developed pulmonary hypertension. Although the elevated pulmonary arterial pressure may have been related to increased pulmonary blood flow, or left sided obstruction, I think it indicates the presence of pulmonary vascular disease. Initially, the cyanosis improved but subsequently she manifested increasing degrees of cyanosis indicating a restriction in the volume of blood flow through the lungs, most likely from changes in the structure of the pulmonary arterial vessels. In my experience, the development of pulmonary vascular disease following a Blalock-Taussig operation is unusual. There are perhaps two explanations for the development of these changes. One is the patient's scoliosis which probably caused restrictive pulmonary disease. It would be helpful to know the Pco₂. I am certain that the impact of scoliosis and resultant reduction in pulmonary volume could have an effect on pulmonary vessels leading to pulmonary vasoconstriction. Certainly, patients with scoliosis may develop pulmonary hypertension and I would think that this process would be accentuated in the face of augmented pulmonary blood flow. The second possibility, though we have no evidence to support it, would be a coexistent condition obstructing pulmonary venous return. Occasionally tetralogy of Fallot may be associated with mitral stenosis or some other obstructive lesion in the left side of the heart which is not manifested until the patient has sufficient pulmonary blood flow. I think this could be a contributing factor

to development of pulmonary hypertension although it would not be severe since the child did not show a pattern of pulmonary edema.

In summary I think the child has the polyplenic syndrome with an endocardial cushion defect and tetralogy of Fallot. The lungs will show occlusive pulmonary vascular disease.

DR VAN TAIL: Thank you Dr Moller. Dr Martin would you please describe the necropsy findings?

DR FRANKLIN H. MARTIN: At necropsy the findings of major significance included both venous and cardiac anomalies.

There was thoracic hypoplasia with the convexity of the spine directed toward the right. The mediastinal structures were shifted slightly toward the left. Each pleural cavity was obliterated by dense fibrous adhesions. Each lung possessed two lobes and the left lung was hypoplastic (Fig. 3). The heart was enlarged with its apex being midline in type. Major anomalies of the systemic veins were present.

Within the heart two complexes were present namely the complete variety of persistent common atrioventricular canal (so-called endocardial cushion defect) and the tetralogy of Fallot.

The former was characterized by (1) a large defect in the lowermost portion of the atrial septum, (2) clefts in the septal tricuspid and in the anterior mitral leaflets yielding a common atrioventricular valve and (3) a defect of the ventricular septum leading to subavalvular interventricular communication (Fig. 4).

Above the atrial septal defect which was part of the persistent common atrioventricular canal the atrial septum showed an additional opening of about 1.0 cm in diameter. This opening was in the position of interatrial ostium II. No distinct fossa ovalis could be identified.

Although the right atrial appendage was somewhat larger than the left each was characterized by being relatively long compared to the width. Muscular ridges were present in each but neither showed features characteristic of pectinate muscles. A small organized thrombus was present in the right appendage (Fig. 4a).

The lining of each ventricle particularly



Fig. 3. Thoracic cavity viewed from in front. The right lung (R.L.) is labeled as the left lung (L.L.). The latter is hypoplastic. The apex of the heart is midline in type.

the left was unusually trabeculated (Fig. 4b). The outflow tract of the right ventricle was narrow by virtue of a vertical crista (Fig. 5a). The narrowed infundibulum led to the pulmonary valve. The latter was bicuspid dome-shaped and highly stenotic (Fig. 5b). Behind the vertical crista the aorta straddled the defective ventricular septum as it arose from both ventricles. Continuity existed between the aorta and the anterior leaflet of the common atrioventricular valve.

Of additional interest were the systemic veins (Fig. 6). The inferior vena cava was abnormal in its course and position. In the abdomen it lay to the left of the aorta (Fig. 6a).

Above the renal veins the inferior cava deviated toward the right but failed to pass through the liver. Instead it entered the right hemithorax to become continuous with the azygos vein. The latter which was unusually wide joined the right superior vena cava (Fig. 6b). The hepatic veins joined to form a common hepatic vein which in turn joined the right atrium where normally the inferior vena cava enters.

There were two superior vena cavae. The left which received the hemiazygos vein joined the left atrium directly (Fig. 6c) and the right entered the right atrium in the usual position. In the superior medi-

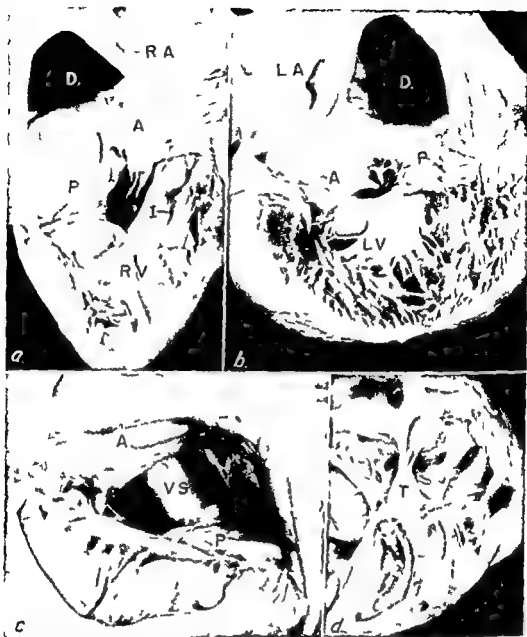


Fig 4 ■ Right atrium (RA) and right ventricle (RV). There is a defect (D) in the lowermost part of the atrial septum representing a characteristic of persistent common atrioventricular canal. Both the anterior mitral and the septal leaflets of the tricuspid valve are cleft yielding a common atrioventricular valve with large anterior (A) and posterior (P) leaflets. The narrow infundibulum (I) of the right ventricle is partially shown as well. b Left atrium (LA) and left ventricle (LV). The large atrial septal defect (D) is apparent as is the common atrioventricular valve. The left ventricular lining is highly trabeculated. c The common atrioventricular valve viewed from above after the atrial septum has been deflected toward the left. Beneath the common atrioventricular valve which includes large anterior (A) and posterior (P) leaflets, the crest of the subjacent ventricular septum (VS) is apparent. d Right atrial appendage. Although the lining is trabeculated the features are not those characteristic of pectinate muscles. Also a focus of organized thrombus (T) is present.

istimium a small vein bridged the two superior vena cavae. No coronary sinus was present (the usual situation when the left superior vena cava enters the left atrium).

The cardiovascular anomalies observed are summarized in diagrammatic form in Fig 7.

There was a functioning B-block I was seen anastomosis between the right subclavian and right pulmonary arteries. Each major pulmonary artery was markedly dilated and thin walled. In addition multiple small aneurysms were present in the pulmonary trunk and in the proximal por-

tions of each of its main branches. In the left pulmonary artery there was an organized embolus represented by a fibrous strand attached to the wall near the junction of the ductus arteriosus. The latter was represented by a ligament.

Each lung had the fundamental structure of a left lung. In addition to the lungs being lobed in each the pulmonary artery passed superior to a main stem bronchus to hook behind the bronchus of the upper lobe and descend into the lower lobe. In addition the distance between the crura and the first division of each main bronchus was the same on the two sides. Two pulmonary veins from each lung were identified. Each joined the left atrium.

Other than the inferior vena cava no abnormal position of the abdominal organs was described. The spleen was peculiar in that there was a main globular 340 gram mass and three accessory masses the largest of which was 2.5 cm in diameter. The uterus was bicornuate with the left horn larger than the right.

Histologic examination of the lungs revealed similar appearances bilaterally. The large muscular arteries showed a varying picture. Some vessels of this class showed medial hypertrophy while others were thin walled.

Muscular arteries both small and large focally showed intimal fibrous thickening including degrees wherein severe luminal obstruction resulted (Fig 8). No plexiform or dilatation lesions were observed.

DR VAN TASSEL: Dr Edwards would you present a closing summary of this interesting case?

DR JESSE E. EDWARDS: A pivotal point for discussion in this case is the phenomenon of continuity of the inferior vena cava with the azygos vein while the right atrial ostium of the inferior vena cava is the opening of a common hepatic vein. This arrangement is observed in this case is highly suggestive perhaps diagnostic of the polysplenic syndrome.¹²

As far as I am aware the first reported example of continuity of the inferior vena cava with the azygos vein in association with polysplenia was presented by Abernethy in 1793.¹

There are two splenic states each of



Fig 5 a Right ventricle (RV) and aorta (A). The aorta straddles a large ventricular septal defect (D) as it arises from both ventricles. The aortic valve is continuous with the anterior leaflet of the common atrioventricular valve. The infundibulum (I) of the right ventricle is narrowly by virtue of a prominent vertical crista (C) which contributes to the narrowness of the infundibulum. The infundibulum leads to the pulmonary valve which is out of view in this illustration. b Unopened pulmonary valve from above. The valve is cupid dome shaped and highly stenotic.

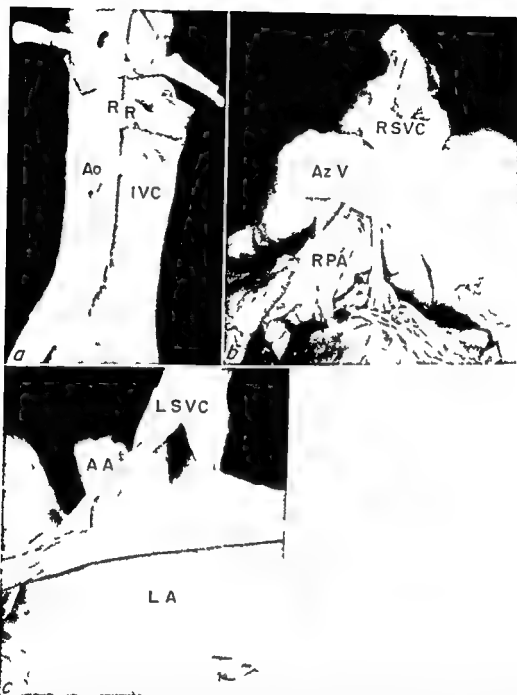


Fig. 6 Systemic veins. *a* Abdominal portion of aorta (Ao) and inferior vena cava (IVC). The latter lies in an abnormal position to the left of the aorta. In the upper abdomen above the renal veins (RR = right renal vein) the inferior vena cava deviates toward the right. It becomes continuous with the azygos vein. *b* The mediastinal structures viewed from the right showing the large azygos vein (Az V) which joins the right superior vena cava (R SVC). The latter in turn joins the right atrium. The right pulmonary artery (RPA) is also in view and shows major dilatation incident to the Blalock-Tausig anastomosis which had been made to this vessel. *c* Continuity of the left superior vena cava (L SVC) with the left atrium (L A). The opening lies near the base of the left atrial appendage (AA).

which tends to be associated with certain types of cardiovascular anomalies. These are the asplenic syndrome and the polysplenic.

The asplenic syndrome has been identified with "bilateral rightsidedness."⁴⁵ In this each lung possesses three lobes and

the intrinsic structure of a right lung.⁴⁶ Each atrial appendage resembles a right atrium and sinoatrial nodes are found bilaterally.⁴⁷ The two lobes of the liver tend to be of equal size. Abdominal heterotaxia including a right-sided stomach and malrotation of the bowel is common.⁴⁸

Cardiovascular anomalies usually include a single atrium with both atrial appendages having the characteristics of the right appendage. The great vessels are usually transposed and a single ventricle is common. There is usually a common atrioventricular valve. Bilateral superior vena cavae are commonly present and frequently the pulmonary veins terminate anomalously in a systemic vein. Pulmonary stenosis is usually present.

The polysplenic syndrome has features which favor a designation of bilateral left sidedness.⁸ This, as in the case presented, is represented by bilobed lungs bilaterally. Each atrial appendage tends to have the appearance of a left appendage. In the atrial septum foramen ovale is usually not identified suggesting absence of septum.¹¹

In general in polysplenia the heart is less primitive than in a plenia. Transposition of the great vessels and pulmonary stenosis are usually absent.

Malposition of the organs is common. In a study of 12 cases from our laboratories Dr. Moller and associates⁸ found the following distribution of organ orientations: situs solitus 4 cases, situs inversus 5 cases, and mixed situs 3 cases. The latter designation was used for situations in which the position of certain organs was discordant with the remainder. In the case here discussed mixed situs may be said to have been present on the basis of a left-sided abdominal inferior vena cava while the other organs were in normal positions.

The midline apex seen in the current case is common in polysplenia. Union of the left superior vena cava with the left atrium was seen in 4 of Moller's 12 cases while the presence of a persistent common atrioventricular canal was also seen in 4 of Moller's cases (not necessarily coinciding with union of the left superior vena cava with the left atrium).

While the pulmonary veins terminated normally in the current case, anomalous termination of pulmonary veins to the right atrium is common in polysplenia. In Moller's reported cases 10 of 12 cases showed such anomalous arrangement (4 total 6 partial).

The tetralogy of Fallot as other forms of pulmonary stenosis is uncommon in

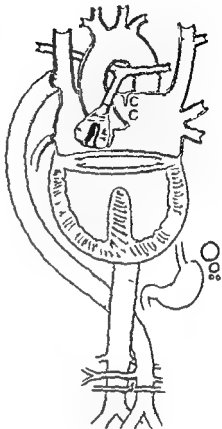


Fig. 7 Summary of cardiovascular anomalies observed

association with polysplenia. Nevertheless the association of the tetralogy with persistent common atrioventricular canal (endocardial cushion defect) is uncommon but not rare.¹⁰ Rao, Anderson, and Edwards¹¹ observed three such combinations among 83 specimens from patients with the tetralogy of Fallot.

In general this association is in a way advantageous in that the pulmonary stenosis of the tetralogy protects the lungs from the effects of the interventricular communication of the endocardial cushion defect. In the case presented the pulmonary stenosis, particularly at valve level, was severe and represented a dominant lesion as evidenced by the prominence of cyanosis.

Finally, a feature of additional interest was the documented pulmonary hypertension in the presence of the functioning Blalock-Taussig anastomosis. While the



Fig 8 Photomicrograph of intrapulmonary arteries. *a* The larger vessel which is a large muscular artery shows a thin wall while the smaller vessel being a muscular arteriole shows intimal fibrous proliferation (Elastic tissue stain $\times 75$). *b* A large muscular artery shows medial hypertrophy and focal intimal proliferation (Elastic tissue stain $\times 60$). *c* A large muscular artery shows irregular medial hypertrophy and moderate intimal proliferation (Elastic tissue stain $\times 60$). *d* A large muscular artery shows medial hypertrophy and virtual occlusion of the lumen by non-specific intimal fibrous proliferation (Elastic tissue stain $\times 100$).

kyphoscoliosis may have contributed to this abnormality, it is probable that the shunt was influential as the important basis for pulmonary hypertension. The occlusive pulmonary vascular disease observed at necropsy was of such nature not usually seen in kyphoscoliosis. It is our view that these lesions complicated the increased

pulmonary flow resulting from the surgical anastomosis.

In other patients without skeletal thoracic disease we have observed similar and more severe occlusive pulmonary vascular lesions following creation of a systemic pulmonary anastomosis for congenital pulmonary stenosis.¹

Final diagnosis

The final diagnosis was polysplenia with endocardial cushion defect and tetralogy of Fallot.

We are indebted to Dr. John T. Eltrom for the specimen of the thoracic organs and major blood vessels and for the description of the roentgen findings.

REFERENCES

1. Anderson R C, Adam L Jr and Burke H. Anomalous inferior vena cava with associated transposition (Intrahepatic interruption of the inferior vena cava). Report of 15 new cases. *J Pediatr* 59:1370 1961.
2. Onley L A, Titus J L, Hickey G H, Rahimtoola S H, Matlin W J and Edwards J E. Anomalous connection of pulmonary veins to right atrium associated with anomalous inferior vena cava situs inversus and multiple spleens (Developmental complex). *Mayo Clin Proc* 40:609 1965.
3. Abernethy J. Account of two instances of uncommon formation in the viscera of the human body. *Philosophical Transactions of the Royal Society London* 83:59 1793.
4. Ivemark L. Implications of agenesis of the spleen on the pathogenesis of ecto-truncus anomalies in childhood. Analysis of the heart malformations in the plenic agenesis syndrome with fourteen new cases. *Acta Paediatr* 44 (Suppl 104):1 1955.
5. Ruttenberg H D, Newfeld H N, Luca L A Jr, Cary L S, Altmann L Jr, Anderson R C and Edwards J E. Syndrome of congenital cardiac disease with asplenia. Dysfunction from other forms of congenital cyanotic cardiac disease. *Amer J Cardiol* 13:187 1964.
6. Brindt H M and Nelson A A. Right pulmonary isomerism associated with venous plenic and other anomalies. *Lab Invest* 14:69 1958.
7. Van Mierop L H S, Patterson L I and Reynolds R W. Two cases of congenital asplenia with isomerism of the cardiac atria and the symmetrical lungs. *Amer J Cardiol* 13:107 1964.
8. Farde W J and Finlay N. Roentgenographic features of asplenia and tetralogy syndrome of visceral asymmetry. *Amer J Roentgenol* 86:15 1961.
9. Muller J H, Nishikawa A, Anderson R C and Edwards J E. Congenital cardiac disease associated with polysplenia. A developmental complex of bilateral left-sidedness. *Circulation* 26:189 1967.
10. Benjamin J F, Landt H and Zerk J. Perforated ostium atriocentricum in a heart which functioned as a fibrous cyst. Report of a case including autopsy in an 18-year-old girl. *Amer Heart J* 19:606 1940.
11. Rao R N S, Anderson R C and Edwards J E. Anatomic variation in the tetralogy of Fallot. *Amer Heart J* 81:361 1971.
12. Wagenvoort C A, D'Silva J W and Edwards J E. Cardiac clinics 131. Hypertensive pulmonary arterial lesions as a late result of anomalies of systemic and pulmonary circulation. *Mayo Clin Proc* 35:186 1960.

Incidence of persistent atrial fibrillation and conduction defects in coronary heart disease

G Orndahl MD

O Thulestius MD

B Hood MD

Göteborg, Sweden

Coronary heart disease (CHD) has often been regarded as a common etiological factor of atrial fibrillation and conduction defects.¹⁻³ There are however only a few reports which actually give the frequency of such disturbances in large populations of coronary heart disease.⁴⁻⁷

In order to test this theory, we have studied 916 patients with coronary heart disease during observation periods of from 1 to 17 years. In this group of patients we have analyzed the frequency of persistent atrial fibrillation and atrioventricular (A-V) and intraventricular conduction defects and have tried to assess their etiology and their prognostic importance.

Patient series

The present assemblage of 916 cases comprises patients from two clinical groups: (1) 444 patients (214 women and 230 men) with hypercholesterolemia and coronary heart disease either proved myocardial infarction or clear cut effort angina or both and (2) 472 (54 women and 418 men) patients below the age of 51 years with myocardial infarction.

For the diagnosis of hypercholesterolemia we required two cholesterol determinations with values above 300 mg per cent and/or the presence of tendinous xanthomas. For details of selection and clinical and biochemical assessment reference is made to our earlier study⁸ from which patients in the present study were taken. The mean age in this group was 67 years (range 35 to 86 years).

Patients with myocardial infarction in early age have been thoroughly described elsewhere and those data represent a follow up study.⁹ As might be expected, a number of patients in this second group also had hypercholesterolemia. However, no patient appears in both groups. The mean age at follow up was 50 years (range 28 to 61 years). Fig. 1 represents an illustration of the entire patient series (groups 1 and 2) in terms of sex and age and the incidence of atrial fibrillation, bundle branch block and A-V block.

Methods

In most cases the electrocardiogram (ECG) was recorded with a four-channel

From the First Medical Department and the Department of Clinical Physiology, Sahlgrenka Hospital, University of Göteborg, Göteborg, Sweden.

This study was supported by a grant from the Swedish National Association of Heart and Chest Disease.

Received for publication May 31, 1974.

Reprint requests to Dr. O. Thulestius, Department of Clinical Physiology, Central Hospital, Växjö, Sweden.

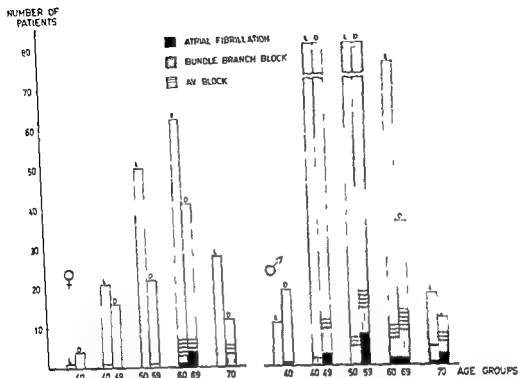


Fig 1 Total patient series accord to sex and age with incidence of atrial fibrillation, bundle branch block and A V block among living and dead in different age groups. ♀ = women, ♂ = men. L = living patients, D = deceased patients.

direct writing electrocardiograph Flma No 42 in the first few years of the study only three extremity leads and an IV R lead were used. Later four precordial R leads and three unipolar leads (aVR , aVL and aVF) were added.

Atrial fibrillation was recognized according to the usual criteria—absolutely irregular ventricular complexes together with fibrillation waves at a frequency above 350 per minute. Bundle branch block and A V block have been defined according to the Minnesota code.¹⁰ Unspecified bundle branch block corresponds to intraventricular block of the Minnesota code.

ST T changes indicative of coronary insufficiency and/or of left ventricular strain have not been separated but have been assembled together in one group and labelled as coronary insufficiency. Digitalis influenced ST T changes labelled as coronary insufficiency must have occurred in fewer than 1 per cent of the cases.

For the ECG diagnosis of myocardial infarction we have required pathological Q

and QS complexes and/or abnormal progression of R waves in precordial leads. ECGs with changes indicative of both coronary insufficiency and infarction have been assigned to the latter group. We were able to reinvestigate the majority of patients in this study. In those who could not be reached or had died the final ECG recordings were traced and examined. The observation time for each patient was calculated as from the time of original diagnosis to the date of the latest follow up ECG. Each instance of ECG abnormality such as atrial fibrillation, bundle branch block or A V block was traced back to determine the time of onset and the possible clinical cause. Only persistent alterations of at least one week's duration were accepted. Among those who died during the time of observation an ECG had been recorded in 52 per cent in the final 2 months of life. In 21 per cent an ECG had been taken 2 to 12 months before death and in the remaining 27 per cent an ECG had been made more than 12 months before death. In the groups of

Table I Survival in relation to ECG signs of coronary heart disease for women and men

Variables	Normal		ECG diagnosis						Totals
			Coronary insufficiency		Myocardial infarction suspected		Myocardial infarction proved		
	Women	Men	Women	Men	Women	Men	Women	Men	
	Living	71	115	45	42	7	23	35	
Dead	9	18	22	37	9	20	51	147	313
Total	80	133	67	79	16	43	86	319	823

Table II Survival in relation to atrial fibrillation and conduction defects for women and men

Variables	ECG diagnosis										Totals
	Atrial fibrillation*		Bundle branch block						II block I + III*		
			Left*		Right		Unspecified				
Women	Men	Women	Men	Women	Men	Women	Men	Women	Men		
Living	1	3	1	4	—	6	1	6	1	5	30
Dead	4	17	4	17	2	8	—	2	3	10	67
Total	5	20	5	21	2	14	1	8	4	15	97

*Two patients with atrial fibrillation and two with AV block also had bundle branch block. These patients are therefore listed twice.

patients who died we have analyzed the heart weight in the autopsied cases. In about 90 per cent of the cases coronary heart disease was the main cause of death.

Results

In Table I the frequency of various ECG signs (normal ECG, coronary insufficiency, suspected myocardial infarction and proved myocardial infarction) have been arranged in relation to survival.

Atrial fibrillation and conduction defects were found in a total of 97 ECGs of 93 patients. Four patients, two men with atrial fibrillation and two with A-V block, also had left bundle branch block.

For the patients with atrial fibrillation and conduction defects, the ratio of women to men was 1:4, whereas this ratio was 2:5 for the whole study group (Table II).

Below the age of 50, 1 woman out of 42 had such ECG changes. In the 50 to 60 year age group, 1 woman out of 72 had the ECG changes. In the 60 to 70 year age group, 1 woman out of 9 was so affected, and in the 70 to 80 year group, 1 woman out of 10 exhibited the changes. The results can be compared to those recorded for the men in our patient series: below the age of 50, 1 man out of 19 presented such ECG changes. In the 50 to 60 year age group, 1 man out of 11 had these ECG changes, in the 60 to 70 year age group, 1 man out of 6 was so affected, and in the 70 to 80 year group, 1 man out of 3 exhibited the changes. These data proved conclusively that men had fibrillation and conduction defects earlier and more frequently than women.

It is apparent from Fig. 1 that there was

Table III Etiologic factors of probable importance in relation to ECG findings

Probable or possible etiology	Diagnosis				
	Atrial fibrillation	Bundle branch block			1:1 block
		Left	Right	Unspecified	
Thyrotoxicosis	1 (4)	—	—	—	—
Rheumatic valvular disease	11 (44)	11 (4)	—	—	11 (5)
Signs of coronary heart disease (CHD) prior to AF and CD	12 (48)	19 (73)	10 (67)	8 (89)	14 (44)
CHD only	6 (24)	17 (46)	11 (37)	7 (48)	8 (47)
CHD with hypertension	6 (24)	4 (97)	4 (75)	1 (11)	6 (37)
AF and CD prior to signs of CHD	—	5 (19)	3 (19)	—	3 (17)
Unknown if signs of CHD or AF and CD appeared first	1 (4)	1 (4)	3 (19)	1 (11)	1 (5)
Total	25	26	16	9	19

† Total number of atrial fibrillation (AF) and conduction defect (CD) = 97
 ‡ Rhythmic disorders only

a high mortality rate in the patients with these ECC changes 66 per cent of the women and 65 per cent of the men had died at the end of the observation period as compared to the rate of about 40 per cent for the total study group. The highest mortality rate was present in those patients with atrial fibrillation and the lowest rate was observed in those with unspecified bundle branch block; these percentages were 84 and 22 respectively.

Definite ECG evidence of myocardial infarction was present in cases with atrial fibrillation or with conduction defects in 50 per cent of both women and men; the same incidence for both sexes also applies to the whole study group.

Possible etiological factors have been listed in Table III. Thyrotoxicosis and rheumatic valvular disease are clear-cut etiological factors. These factors also apply to a 67-year-old man with left bundle branch block who had syphilitic valvular disease and to a 46-year-old woman with A-V block which could be traced back to an acute episode of rheumatic fever. For the present work we have chosen a high borderline for hypertension i.e. 110 mm Hg diastolic pressure.

In 33 of 94 patients the atrial fibrillation or the conduction defect was present before angina pectoris or myocardial infarction

was diagnosed. As seen in Table III approximately half of the patients with atrial fibrillation had rheumatic valvular disease or thyrotoxicosis.

In those patients in whom the probable etiology was CHD (signs of CHD before atrial fibrillation and conduction defect) the average survival time was shorter than for those patients in whom hypertension was an additional etiological factor. In the former category many patients died within a few months whereas the survival rate for the latter group was usually several years.

Table IV presents the incidence of new cases of atrial fibrillation and conduction defects during the observation time in subgroups of the two parts of the total patient series. The extremely low incidence of these abnormalities in the large category of infarctions in early age should be noted. This means that there was no further incidence of atrial fibrillation and that only four instances of conduction defects were discovered in 275 persons observed during more than 20 000 patient months (approximately 1 to 17 years) after their first myocardial infarction. Another point of interest is the small number of persisting atrial fibrillation and conduction defects as a consequence of acute myocardial infarction (in only 9 out of 61 new cases or 15 per cent).

Table IV New cases of atrial fibrillation and conduction defects during the observation time in terms of clinical groups and number of patients

Clinical groups	No of patients	Total observation time (patient months)	Diagnosis				
			Atrial fibrillation	Bundle branch block			1:1 block
				Left	Right	Unspecified	
Hypercholesterolemia							
Living							
Angina pectoris	142	9 272	1	—	—	—	2
Myocardial infarction	124	8 489	2 (1)*	1	2	1	2 (1)
Died	118	6 919	6 (1)	11 (1)	2	—	7 (1)
Young infarctions							
Living	275	20 678	—	—	1 (1)	4	1
Died	197	5 441	6	4 (1)	3 (2)	2	2
Total	916	50 859	15 (?)	17 (?)	8 (3)	7	14 (?)

*Figures in parentheses indicate the number of cases of acquired fibrillation or block during an episode of acute infarction.

Atrial fibrillation was present in 25 patients or 2.7 per cent of the total patient series. Fourteen of the 21 patients who died were autopsied. In 10 there were signs of old and/or recent myocardial infarction. In 6 of the patients autopsied there was a diffuse fibrosis of large areas of the myocardium and 5 of the 6 had electrocardiographic evidence of myocardial infarction in their final ECG. In the one remaining case there was valid clinical evidence of myocardial infarction. In these six cases mitral stenosis, hypertension or coronary heart disease (in the absence of other factors) were considered as etiological factors.

Left bundle branch block was present in 26 patients or 2.8 per cent of the patient series. Nine of the 21 patients who died were autopsied. All had macroscopic evidence of myocardial infarction and at least two had microscopic evidence of diffuse myocardial fibrosis. The etiology in these two cases was CHD with hypertension, or CHD only.

Right bundle branch block was present in 16 cases or 1.7 per cent of the patient series. Five of the ten patients who died were autopsied. In four there was macroscopic evidence of myocardial infarction and in two cases (one with infarction) there was myocardial fibrosis. The etiology in the latter two cases was CHD only in one

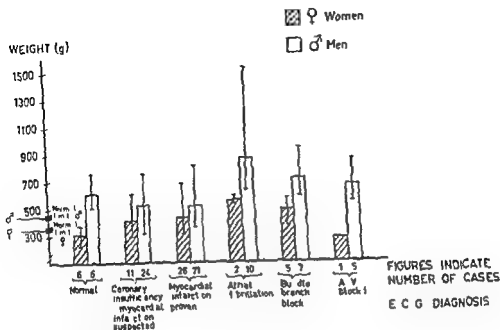
patient and CHD with hypertension in the other.

Unspecified bundle branch block was present in 9 cases or 0.98 per cent of the patient series. One of the two patients who died was autopsied and presented microscopic evidence of myocardial infarction.

First degree A V block was present in 19 patients or 2.1 per cent of the patient series. Eight of the 12 patients who died were autopsied. In five there was microscopic evidence of myocardial infarction and in two cases evidence of myocardial fibrosis. The etiology in these last two was CHD only in one case and hypertension with CHD in the other. No instance of second degree A V block could be found.

Third degree A V block was present in two patients (0.2 per cent of the patient series), both of whom were living at the end of the observation time. The etiology was CHD only in both patients and in one the total A V block began in connection with an episode of acute infarction. No case of Wolff Parkinson White (WPW) syndrome was present in this patient group.

Heart weights are presented in Fig. 2. From the illustration it can be seen that the patients with fibrillation and conduction defects seem to have larger hearts than the patients with normal ECGs or those pa-



FIGURES INDICATE
NUMBER OF CASES
E C G DIAGNOSIS

Fig. 1. Mean heart weights in cases with coronary heart disease classified according to ECG criteria. Bars indicate ranges for men and women.

tients with ECG changes characteristic of coronary heart disease. Furthermore there seems to be a tendency for larger hearts in patients with fibrillation compared to those having conduction defects. No correlation was found between diastolic blood pressure and heart weight. The same general trends which hold for heart weights also apply to heart volumes.

Discussion

The incidence of atrial fibrillation and conduction defects (bundle branch block and atrioventricular block) in various population studies in studies of coronary heart disease and in our present patient series has been given in Table V. The comparison is to some extent invalidated because the criteria for ECG evaluation have by no means been uniform. However the code suggested by Blackburn and associates¹⁰ seems to have been increasingly adopted in recent years.

The lowest incidence of atrial fibrillation and conduction defects was found as expected among visitors in the US Air Force.¹¹ The cases in this study were predominantly all below the age of 50 years.

With continuous ECG monitoring in acute myocardial infarction a greater num-

ber of rhythm and conduction disturbances have been revealed.^{12,13} The studies in patient groups with angina pectoris and/or earlier infarctions are comparatively rare but these studies show a lower frequency of such disturbances than in cases of acute infarction.¹⁴

In the series of 317 patients with coronary heart disease in a population study of 6 672 adults¹⁵ there was a slightly lower incidence of such ECG changes on the whole as compared to the results for our series. The incidence of ECG changes in our study was however lower than the number of such changes found in acute myocardial infarction and in acute myocarditis. The highest frequency of rhythm and conduction defects was found in a study group having myotonic dystrophy.¹⁶

From Table VI it is evident that ECG abnormalities as a rule increase with advancing age. No conclusions have been made from patients below the age of 40 years and above the age of 70 years because of the limited number in each group. These groups have therefore been omitted. In order to facilitate a comparison of our material with the Levenson study¹⁷ we have presented a sex and age matched correlation of patients (both living and

Table V Per cent incidence of certain ECG findings

Authors and year	Type of study	Diagnosis					
		Atrial fibrillation	Bundle branch block		11 block		
			Left	Right	I	II	III
<i>Population studies</i>							
Olander and associates ¹¹ 1965*	5 129 adults in Tecumseh Mich	0.4	0.35	0.35	1.9	0	0.4
Tibblin ¹² 1966*	855 men age 50 years	0.23	0.6	0.7	0.94	0	0
Hiss and Lamb ¹³ 1962	122 043 men U.S. Air Force age 16 to 50 years	0.001	0.013	0.18	0.65	0.006	0.001
<i>Coronary heart disease (CHD)</i>							
Gordon and Grist ⁴ 1965*	317 CHD patients from population study	0.95	2.4	1.9	—	0.0	0.3 [†]
Shanoff and Little ¹⁴ 1965	101 male survivors of infarction Mean observation time 40 months	0	4.0	—	0	0	0
Imperial Carballo and Zimmermann ⁸ 1960	153 patients during acute infarction	9.8	0	7.8	3.3	3.3	—
Anastasiadis and Sivertson ¹⁰ 1961	351 patients during acute infarction	4.7	1.9	4.2	6.3	1.8	2.1
Luck ⁹ 1963	3 174 cases of recent infarction collected from literature	5.0 to 15.0	—	—	—	1.0 to 12.0	1.0 to 3.0
Hurwitz and Eliot ⁵ 1964	500 cases with acute infarction	7.0	—	—	5.0	2.0	2.0
Spinn and associates ¹¹ 1964	30 patients with acute infarction (electronic monitoring)	10.0	7.0	7.0	7.0	7.0	0
Bauer Julian and Valentine ¹⁵ 1965†	100 patients with acute infarction (electronic monitoring)	16.0	7.0	6.0	—	—	8.0
Dix ¹⁶ 1965	126 patients with acute infarction (electronic monitoring)	10.0	6.0	—	—	—	3.0
<i>Miscellaneous</i>							
Iversius and Orndahl ¹⁷ 1965†	250 patients with acute myocarditis	7.0 (50)	7.0 (97)	—	18.0	5.0 (77)	4.0 (73)
Orndahl and associates ¹⁸ 1964	29 patients with dystrophic myocarditis	20.0	7.0	—	28.0	—	—
<i>Present study</i>							
	164 women alive	0.6	0.6	0	1.6	0	0
	104 women dead	3.8	3.8	1.9	2.9	0	0
	377 men alive	0.8	1.1	1.6	0.8	0	0.53
	271 men dead	6.3	6.3	3.0	3.3	0	0
	916 patients (total number)	2.7	2.8	1.7	2.1	0	0.22

*Classified according to Blackburn and associates (1960)

†Bundle branch block persisted in 3 patients

‡Figures in parentheses indicate per cent persistent changes after 6 months

Table VI Per cent ECG findings according to age and sex in the Tecumseh¹ and in the present study

Variables	43 to 49 years		50 to 59 years		60 to 69 years	
	Women	Men	Women	Men	Women	Men
Atrial fibrillation						
Tecumseh study	0.1	0	0.9	0	0.5	2.3
Present study	0	0	0	0	1	7.7
Living	0	1.0	0	5.6	8.8	4.5
Dead						
Left bundle branch block						
Tecumseh study	0	0.7	0.6	0.9	0	1.1
Present study	0	0	0	0.6	1.6	7.7
Living	0	3.0	0	5.0	7.7	8.1
Dead						
Right bundle branch block						
Tecumseh study	0	0	0.6	0.1	0.5	1.7
Present study	0	1.0	0	0.6	0	1.3
Living	0	3.2	0	1.6	2	4.1
Dead						
1:1 block						
Tecumseh study	0.6	1.5	7.1	1.1	4.1	4.5
Present study	4.5	0	0	0.6	3	2.7
Living	0.7	1.0	2.8	3.0	7.6	8.1
Dead						

dead) in our study group with the patients in that study (see Table VI).

A comparison of our patient series having coronary heart disease with a population study of normal individuals reveals a striking similarity with respect to the incidence of atrial fibrillation and conduction defects. This is especially valid for the most comparable groups of our living patients and those from the Tecumseh study.¹⁷ The similarity is somewhat astonishing in view of the fact that our study represents a long term follow up (more than 50 000 patient months) compared with the one shot survey of Tecumseh. This certainly does not favor the opinion that CHD is a main causative factor for atrial fibrillation and conduction defects. This conclusion is also supported by the observation of only one new case of atrial fibrillation or conduction defects appearing in about 450 patient months (see Table IV). Moreover it is interesting to mention that only 3 patients out of 774 (1.2 per cent) had persistent disturbances (AF + block) after acute

infarctions (atrial fibrillation 0.3 per cent, bundle branch block 0.6 per cent, AV block 0.3 per cent). In this connection it should be noted that therapeutic measures such as the successful conversion of atrial fibrillation have not been applied in our patient series.

The various possible etiological factors in our study group and in a similar survey from the literature are presented in Table VII. A comparison of the different studies is somewhat difficult because there was no uniform definition of hypertension and coronary heart disease. We started with a patient group having coronary heart disease whereas other investigators began with a selection of patients with atrial fibrillation and conduction defects. There is a fairly good agreement between our etiological classification for atrial fibrillation and bundle branch block and that of the other studies.

The results from these comparisons do not therefore indicate coronary heart disease to be of such etiological importance for

Table VII Per cent etiologic distribution in atrial fibrillation and conduction defects

Variables	Atrial fibrillation			Conduction defects	
	Sokolow and Ball ² 1956	Rikseth and Morstein ²³ 1963	Hurst and associates ²⁴ 1964	Left	
				Johnson and associates ²⁵ 1951	Seitz ²⁶
Thyrotoxicosis	6.0	5.0	4.0	—	—
Rheumatic heart disease	53	55	70	6	8
Hypertension only	12	10	11	40	4
Coronary heart disease (CHD)	21	20	47	35	11
CHD only	—	—	35	14	31
CHD with hypertension	—	—	12	21	41
Acute myocardial infarction	—	—	—	—	—
Miscellaneous	8	10	19	17	16
Total number	177	274	230	555	93

*Cited from Friedberg and associates⁴¹ 1963

atrial fibrillation and bundle branch block as this has been commonly assumed.

As regards first degree A V block there are definite discrepancies between the patient series of Logue and Hanson¹⁸ and our study group regarding possible etiologic factors with a higher rate of coronary heart disease appearing in our group. It is difficult however to speculate about the reasons for this.

We had only two patients with third degree A V block and no patients with second degree A V block. This very low frequency does not seem to point to coronary heart disease as an important etiologic factor for second and third-degree A V block although higher frequencies are reported by others (see Table VII).

It is a time honored observation that patients with atrial fibrillation seldom develop coronary heart disease.^{18, 19} The experience gained from our study seems to make the inverse hypothesis possible, namely that coronary heart disease fairly seldom leads to atrial fibrillation and that coronary heart disease is an uncommon etiologic factor of atrial fibrillation (1.3 per cent in our study group). Analogous to this Holzmüller¹⁹ only found 5 instances of atrial fibrillation in 500 patients with angina pectoris.

Atrial fibrillation does not always imply histological evidence of atrial damage since Soderstrom¹ did not find a strong correlation between these two conditions in 40 patients of histologically proved atrial infarction. However James²⁷ in a detailed anatomical study of the atrial blood supply in 11 cases of acute myocardial infarction with atrial rhythm disturbances found a coronary occlusion proximal to the origin of the sinus node artery and signs of infarction in the sinus node area. In a case of idiopathic atrial fibrillation of twenty years duration Cancelli and Nicolussi²⁸ described an occlusion of the sinus node artery. Varghese⁴ however found no sinus node artery changes on coronary angiography in some cases of atrial fibrillation of this type. Thus there is still a great deal of controversy as to the vascular origin of atrial fibrillation.

Anatomically even minor changes in involving a small area of the myocardium containing Purkinje fibers might give rise to an interruption of the specialized conduction pathways with resulting conduction defects. Therefore it should *a priori* be expected that coronary heart disease with even small infarctions was a frequent cause of bundle branch block. This however has not been proved. The reason for this might

A V block					
Right	First degree		Third degree		
	Loague and Hinton 1941	Penton and associates ⁸ 1956	Race and White ¹⁰ 1958	Cu d and associates ⁹ 1967	Friedberg and associates ⁷ 1967
en vas and after ¹¹ 1950					
—	—	—	—	—	—
8	78	8	8	10	6
20	1	25		8	5
31	14	43	73	17	(4)
—	—	21	35	11	18
—	—	—	23	—	10
—	—	19	11	25	1
38	57	21	19	45	29
281	100	251	218	130	100

be twofold. First, it is known that the ventricular septum has a very rich blood supply with septal branches from both the left and the right coronary artery.¹² This is the basis for the high degree of potential collateral channels which can secure blood flow even in cases with extensive luminal changes. Second, recent electrophysiological studies⁴ seem to indicate that Purkinje fibers actually are more resistant to hypoxia than ordinary myocardium. It may therefore not be surprising to find a rather low frequency of conduction defects in the present study group of selected patients with coronary heart disease.

A striking feature in the autopsied cases was the high incidence of diffuse myocardial fibrosis. This finding was present in 50 per cent of the cases, both isolated and in conjunction with myocardial infarction. The question therefore arises if diffuse myocardial fibrosis might be of specific importance for the development of atrial fibrillation or conduction defects. It may be worthwhile to investigate this problem further with more refined anatomical techniques.

Another important observation was the marked correlation between heart weight and volume and the incidence of atrial fibrillation. In the present patient series most cases of atrial fibrillation occurred in

patients with a heart weight of 550 Gm or a heart volume above 600 ml per square meter of body surface area. This is in agreement with electrophysiologic studies on smooth muscle and atrial strip preparations in which electrical activity was directly proportional to external tension.^{27,28}

In the present study it was rather striking that atrial fibrillation or conduction defects develop at a late stage of CHD, namely a few months to two years before death. However, there is a better prognosis in atrial fibrillation due to thyrotoxicosis, rheumatic heart disease and myotonic dystrophy.

Summary

Permanent atrial fibrillation and conduction defects (bundle branch block and A V block, classified according to Blackburn and associates¹⁹) have been studied in a patient series of 916 patients with coronary heart disease.

The following results were obtained:

Incidence. The frequency of atrial fibrillation, left and right bundle branch block and first-degree A V block was about 2 per cent. A sex and age matched correlation of the incidence of these disturbances in our study group with a population study showed astonishing similarities. Further

more, there was a very low rate of new cases of atrial fibrillation and conduction defects in our patients (1 new case for 70 patient years). Moreover only 0.3 per cent of these disturbances persisted after an episode of acute myocardial infarction.

Mortality and prognosis. The mortality rate for patients with atrial fibrillation and conduction defects was nearly twice as high as that of the whole study group. The death rate was especially high for patients with atrial fibrillation and left bundle branch block. The average survival time varied from a few months to two years for most patients with atrial fibrillation, bundle branch block, and first degree A-V block when the probable etiology was coronary heart disease.

Etiology. The analysis of possible etiological factors in the present study of atrial fibrillation and bundle branch block showed approximately the same distribution and frequency compared to other studies of large patient series in the literature.

The result of this study does not support the widespread opinion that coronary heart disease is the predominant cause of atrial fibrillation and conduction defects, because this outcome was seldom found and rarely developed in our follow up study of 916 patients with coronary heart disease. Future studies should therefore be directed to look for alternative etiological factors.

REFERENCES

1. Friedberg C K. Diseases of the heart. Philadelphia and London 1951. W. B. Saunders Company.
2. Mulcahy R, Hickey N, and Maurer B. Aetiology of bundle branch block. *Br Heart J* 30:34 1968.
3. Wood P. Diseases of the heart and circulation. London 1959. Pyre & Spottiswoode Ltd.
4. Gordon T, and Grist C C. Coronary heart disease in adults. United States 1960-1962. Data from the National Health Survey. Washington 1965. U.S. Govt. Printing Office.
5. Hurwitz M, and Eliot R S. Arrhythmias in acute myocardial infarction. *Dis Chest* 45:616 1964.
6. Imperial E S, Carballo R, and Zimmerman H A. Disturbances of rate rhythm and conduction in acute myocardial infarction. A statistical study of 153 cases. *Am J Cardiol* 24:24 1960.
7. Pick A. Cardiac arrhythmias associated with recent myocardial infarction. In Likhoff W, and Moyer J H, editors. Coronary heart disease. The seventh Hahnemann symposium. New York and London 1963. Grune & Stratton, Inc. p. 247.
8. Hood B, Sjöström H, Örndahl C, Ahlström M, and Welin G. Long term prognosis in myocardial hypercholesterolemia. The effect of strict diet. *Acta Med Scand* 178:161 1965.
9. Hood B, Tibblin G, Welin G, Örndahl G, and Korsén Bengtsson K. Myocardial infarction in early age. Coronary risk factors and their deficient control. *Acta Med Scand* 185:241 1969.
10. Blackburn H, Keys A, Simonson E, Rautaharju I, and Punsir S. The electrocardiogram in population studies. A classification system. *Circulation* 21:1160 1960.
11. Hiss A G, and Lamb I E. Electrocardiographic findings in 12,204 individuals. *Circulation* 26:947 1962.
12. Bauer G E, Julian D G, and Valentine P A. Bundle-branch block in acute myocardial infarction. *Br Heart J* 24:774 1965.
13. Day H W. Effectiveness of an intensive coronary care unit. *Am J Cardiol* 15:51 1965.
14. Sprain J I, Moellering K C, Jr, Haber E, and Wheeler E O. Arrhythmias in acute myocardial infarction. *New Engl J Med* 271:427 1964.
15. Shinnoff H M, and Little J A. Studies of multiple survivors of myocardial infarction. VI. The electrocardiogram. *Can Med Assoc J* 93:1049 1965.
16. Örndahl G, Thulesius O, Eneström S, and Dehlin O. The heart in myotonic disease. *Acta Med Scand* 176:419 1964.
17. Ostrander L D, Brandt R I, Kjølberg M O, and Epstein I H. Electrocardiographic findings among the adult population of a total natural community—Tecumseh, Michigan. *Circulation* 31:888 1965.
18. Lague R B, and Hanson J F. Heart block. A study of 100 cases with prolonged P-R interval. *Am J Med Sci* 207:78 1944.
19. Holzmair M. Klinische elektrokardiographie. Fifth edition. Stuttgart 1965. Georg Thieme Verlag.
20. Kitz I N, and Pick A. Clinical electrocardiography. Part I. The arrhythmias. Philadelphia 1956. Lea & Febiger Publishers p. 393.
21. Söderström N. Myocardial infarction and mural thrombosis in the atria of the heart. *Acta Med Scand* (Suppl.):17 1948.
22. James T N. Myocardial infarction and atrial arrhythmias. *Circulation* 24:761 1961.
23. Cancelli I A, and Nickluis, T M. Atrial fibrillation with occlusion of the sinus node artery. *Arch Intern Med* 117:427 1966.
24. Virmasvaks E. Personal communication.
25. Ivaldi S. Coronary angiography. A technical, anatomic and clinical study. *Acta Radiol* (Suppl.) 233 1964.
26. Bagdinos A A, Stuckey J H, Ilera J, Amer N S, and Hoffman B F. Effects of ischemia and hypoxia on the specialized conducting system of the canine heart. *Am Heart J* 61:206 1961.
27. Axelsson U. Personal communication.
28. Deck K A. Dehnungseffekte am spontanen ch

- legenden isolierten Sinusknoten Pfluegers Arch. 280:170 1964
- 29 Tibblin G Personal communication
- 30 Anastasiadis C T and Sivertson S E Myocardial infarction—A ten year experience in a Midwestern general hospital Ann Intern Med 50:749 1961
- 31 Levander Lindgren M Studies in myocarditis II Electrocardiographic changes Card ologia 47:73 1965
- 32 Sokolow M and Bail R E Factors influencing conversion of chronic atrial fibrillation with special reference to serum quinidine concentration Circulation 14:568 1956
- 33 Rolseth R and Storstein O Quantitative therapy of chronic auricular fibrillation Occurrence and mechanism of syncope Arch Intern Med 111:184 1963
- 34 Hurst J W Paulk E A Proctor H D and Schlant R C Management of patients with atrial fibrillation Amer J Med 37:728 1964
- 35 Johnson R P Messer A L Shreenivas B A and White P D Prognosis in bundle-branch block II Factors influencing the survival period in left bundle-branch block AM HEART J 41:725 1950
- 36 Scott P C Left bundle-branch block—A clinical assessment Part I AM HEART J 70:535 1965
- 37 Shreenivas B A Messer A L Johnson B P and White P D Prognosis in bundle branch block I Factors influencing the survival period in right bundle branch block AM HEART J 40:891 1950
- 38 Penton G H Miller H and Levine S A Some clinical features of complete heart block Circulation 13:801 1946
- 39 Rowe J C and White P D Complete heart block A follow up study Ann. Intern Med 49:260 1958
- 40 Curd G W Jr Dennis E W Jordan J McNamara D Montero A C Peterson P K Prutt R D and Schnur S Etiology of atrioventricular heart block A study of its relevance to prognosis and pacemaker therapy Cardiovasc Res Cent. Bull 1:63 1963
- 41 Friedberg C K Donoso E and Stein W G Nonsurgical acquired heart block Ann. N Y Acad Sci 111:1835 1964
- 42 James T N Anatomy of the coronary arteries New York 1961 Paul B Hoeber Inc.

The medical treatment of angina pectoris II. Design of an antianginal drug study

Wilbert S. Aronow, M.D.*
Long Beach and Irvine, Calif.

The evaluation of an antianginal drug is very difficult for many reasons. Spontaneous remission or exacerbation of angina may occur. Placebo may cause improvement of exercise performance as well as relief of pain.¹ Chest pain due to other coexisting disorders may be interpreted as angina. Changes in the weather, in emotional stress, in the amount of activity, in smoking, in dietary habits, and in concomitant medications are some of the many factors that influence the subjective symptom of anginal pain.

The design of the exercise study used to evaluate an antianginal drug may also prejudice the results. Some of my objections to one such study² include the following. This exercise study was not double blind. Exercise was performed by the patients ascending and descending a two step staircase instead of with a constant load bicycle ergometer which would be associated with a more uniform and reproducible work load. The author states that "After a light break, fast and at a variable interval following the administration of placebo the patient was exercised until he reported the onset of typical anginal pain." As angina is precipi-

tated more readily after exercise in the postprandial state,³ the investigators' patients² would be expected to have a decrease in exercise performance after placebo compared to active drug. Thirty minutes after the first exercise study, active drug was given to all 28 patients on the 3 days they were tested. The first 12 patients received a fixed order of drug administration with isosorbide dinitrate on day 1, propranolol on day 2, and isosorbide dinitrate plus propranolol on day 3. This fixed order of drug administration favors the combination of propranolol plus isosorbide dinitrate since a better exercise performance may result on the third day because of training. The second exercise test on each day occurred after the administration of active drug and was performed in some patients at a time when the improved exercise performance might be due to the warm up phenomenon.⁴

With these variables in mind, the following discussion suggests an approach to the problem of how to design a reliable antianginal drug study.

An adequate number of patients (at least 20) with at least 5 episodes of classic

From the Cardiology Section, Medical Service, Long Beach Veterans Administration Hospital and the University of California College of Medicine, Irvine, Calif.

Received for publication Feb. 7, 1972.

Reprint requests to Wilbert S. Aronow, M.D., Cardiology Section, Veterans Administration Hospital, Long Beach, Calif. 90801.

*Staff Cardiologist and Chief of Phonocardiography, Long Beach Veterans Administration Hospital, Assistant Clinical Professor of Medicine, University of California College of Medicine, Irvine, Calif.

exertional angina pectoris per week for at least 3 months due to coronary artery disease should be evaluated on an outpatient basis. Patients with a classical history of exertional angina pectoris and ischemic S-T segment depression of at least 1 mm on the postexercise electrocardiogram (ECG) may be considered as quite likely to have coronary artery disease. However the presence of a documented myocardial infarction at least 6 months old or the visualization of significant coronary artery disease by coronary angiography better document the presence of coronary artery disease. These patients should be cooperative and able to keep a detailed diary of their anginal episodes and the relationship of these attacks to various precipitating factors. Patients with chest pain due to other conditions such as diaphragmatic hernia, esophagitis, peptic ulcer, cervical arthritis, gallbladder disease, and musculoskeletal disorders should be excluded. Patients with a marked psychogenic overlay of anxiety who construe every minor ache or chest pain as an anginal attack should be excluded. Patients in whom there is a sudden increase in severity and frequency of their angina should be excluded. Patients with other forms of heart disease, uncompensated congestive failure, uncontrolled hypertension or coexisting disorders that may require hospitalization or change in drug therapy should be excluded.

Because of unconscious observer bias an antianginal drug study must be at least double blind. If one is evaluating a drug such as propranolol which slows the heart rate, making it easy for the investigator to detect whether the patient is on active drug or on placebo, other precautions must be taken.^{5,6} In such a study^{5,6} the patients may be followed by cardiac residents in a cardiac clinic. The resting and postexercise ECGs may be taken during the exercise studies by cardiac residents without the investigators knowing what the heart rates were until after the entire study has been completed.

Some investigators object to a fixed dose double blind crossover study because the active drug is not titrated to meet the patient's needs. In addition an initial period of improvement lasting during the

first 11 weeks on the average may occur in an antianginal drug study and this is attributed to the psychotherapeutic effect of increased attention and care inherent in a research program.⁷ Therefore the following protocol is suggested.

During the first 4 weeks of the antianginal drug study the patients should be placed on placebo and an exercise study should be performed on each patient during each week. During weeks 5 through 8 the patients should be placed on different doses of the active drug each week and an exercise study performed each week. During weeks 9 through 12 the patients should again be placed on placebo. In week 13 a double blind crossover study should begin with the dose of active drug being selected on the basis of the exercise studies performed during weeks 5 through 8. The medications should be coded and placebo or drug should be assigned randomly to the patients using a table of random numbers. The same number of placebo and active drug tablets should be given and the placebo should be identical in shape, color, size, and taste to the active drug. After 6 weeks of either drug or placebo there should be a washout period of at least 1 week during which the patients should be placed on placebo, then the patients who received active drug during the first 6 weeks of the double blind crossover study should receive placebo for 6 weeks and the patients who initially received placebo should receive active drug for 6 weeks. Exercise studies should be performed at least 4 times during the last week of the drug and placebo study periods. Appropriate laboratory tests should be obtained during the control drug and placebo periods to determine whether the drug produces any toxic effects.

During the entire study each patient should keep a detailed diary of every anginal episode that occurs and its relationship to precipitating factors. Dietary and smoking habits should remain relatively constant. No other antianginal medication with the exception of nitroglycerin should be taken during the entire drug study. No change in any medication during the double blind crossover study should be made unless absolutely necessary. Tablet counts

should be made after the medication is returned to determine how much medication has actually been taken.

Exercise studies should be performed at a time after medication when the medication is expected to exert its maximum effect. Exercise studies should be performed at least 3 hours after a light meal, at the same time of day and at the same time after the administration of medication during the drug period as during the placebo period and in a room with constant temperature that is neither cold nor hot. We prefer to exercise subjects while they are in an upright position on a constant load bicycle ergometer until the onset of angina. Redwood and his associates⁸ have shown that it is preferable to choose a progressive work load in the control period so that angina will be produced after 3 to 6 minutes of upright exercise. This same work load should be used in the drug period and in the placebo period. Patients should not smoke or take nitroglycerin for at least 2 hours prior to the exercise studies. Patients should be observed taking their medication prior to the exercise studies. Blood pressures and heart rates should be obtained with the patients sitting upright on the bicycle ergometer at rest and immediately after the onset of angina pectoris. ECGs should be taken prior to exercise during exercise and after the onset of angina pectoris.

Finally, the data obtained during the double blind crossover study should be statistically analyzed for each individual patient to see if the active drug caused at least a 50 per cent reduction in anginal episodes, caused a significant improvement in exercise performance, caused a significant improvement in ischemic ST segment depression in the resting exercise or post exercise ECGs or caused a significant in-

crease in the product of systolic blood pressure and heart rate at the onset of angina compared to the placebo. The incidence and severity of any side effects and any abnormal laboratory data should be tabulated for the active drug and for the placebo. If patients drop out of the study the reasons for their doing so should be thoroughly evaluated.

If the data statistically show that the active drug is an effective antianginal agent, and if these data are confirmed by other well-designed studies, then a large scale multihospital cooperative study should be conceived and executed to determine whether this medication will have an effect on longevity and on the incidence of myocardial infarction.

REFERENCES

1. Aronow W S and Chesluk H M. Sublingual isosorbide dinitrate versus sublingual nitroglycerin in angina pectoris. *Circulation* 41: 869, 1970.
2. Russek H I. Propranolol and isosorbide dinitrate synergism in angina pectoris. *Am J Cardiol* 21: 44, 1968.
3. Goldstein R E, Pedwood D R, Roising D R, Besser G D and Epstein S F. Alterations in the circulatory response to exercise following a meal and their relationship to postprandial angina pectoris. *Circulation* 41: 90, 1970.
4. McAlpin R N and Kuttus A A. Adaptation to exercise in angina pectoris. The electrocardiogram during treadmill walking and coronary angiographic findings. *Circulation* 33: 181, 1966.
5. Aronow W S and Kaplan M A. Propranolol combined with isosorbide dinitrate versus placebo in angina pectoris. *N Engl J Med* 280: 41, 1969.
6. Aronow W S and Kaplan M A. Dilemma of angina pectoris. *N Engl J Med* 281: 49, 1969.
7. Cole S L, Kay H and Griffith G C. A study of intravaginal agents. I. A curve analysis of multiple control periods. *Circulation* 13: 40, 1957.
8. Redwood D F, Roising D R, Goldstein R E, Besser G D and Epstein S E. Importance of the design of an exercise protocol in the evaluation of patients with angina pectoris. *Circulation* 43: 618, 1971.

Hazards of central venous pressure monitoring Pericardial tamponade

Local adverse effects such as thrombosis and embolus, suppurative thrombophlebitis, bacteremia, venous necrosis, and venous laceration secondary to central venous pressure monitoring have been widely reported. Hemothorax, pneumothorax, subcutaneous emphysema, brachial plexus injury, and air emboli may have resulted from subclavian venipuncture from central venous pressure (CVP) catheter placement.^{1,2} Shearin of the catheter during placement has caused embolization of catheter fragments.³

Cardiac perforation with pericardial tamponade has only recently been recorded with death occurring in four of the five reported cases.^{4,5} The alarming factor is that three of the five cases were reported in two separate papers from the same institution.^{4,5} The data was readily made in the light of the three patients reported only because this entity had previously been recognized by the thoracic surgeons called in consultation by the attending physicians. This is alarming because the commonly accepted standard for catheter placement and management are exactly the same as those practiced everywhere in the United States. The possibility of death from CVP monitoring itself rather than from the condition for which it is employed must always be considered. It seems probable that some of the hazards of CVP monitoring have been ignored because they have not been recognized.

By placing the catheter using absolutely sterile surgical techniques and applying an antibiotic ointment daily to the insertion site, local infection with subsequent generalized sepsis can be avoided. No medication and only a minimal amount of fluid is infused through the catheter to reduce local and cardiac irritation. The hypovolemic patient is placed in the Trendelenburg position to prevent air embolism. The potential pulmonary complication of subclavicular insertion can be avoided by placement of the catheter in the left median basilic vein.

To minimize the possibility of pericardial tamponade, a diopaque catheter is always used and the catheter is never beveled. The exact location of the radiopaque catheter is confirmed by chest film after placement is estimated by external measurement. The catheter tip is not advanced into the right atrium. The catheter is securely sutured and taped to prevent advancement.

Cardiac tamponade can occur shortly after placement or may take 24 to 48 hours before it occurs,

however, the longer the catheter is left in the patient the greater the risk and the greater the incidence of all complications.

Pericardial tamponade secondary to the CVP catheter may be rare but it is extremely serious when it occurs. Where rapid deterioration is noted in any patient with a CVP catheter in place, confirmation of the position of the catheter tip radiographically is mandatory. If there are any signs radiographically or clinically of pericardial tamponade, pericardiocentesis may be therapeutic as well as diagnostic.

It is axiomatic that the physician must always consider the benefits and hazards of any form of management of the patient whether it be diagnostic, therapeutic, or surveillance. He must continuously be aware of all the known and possible complications of his endeavors. This is particularly true of CVP monitoring where the hazards if they go unrecognized greatly outweigh the benefits.

Howard D. Holmesley MD

John S. Zelenik MD

Department of Obstetrics and Gynecology
Vanderbilt University School of Medicine
Nashville, Tenn. 37203

REFERENCES

1. Bansner G, Keith D and Terluk H. Complications following use of indwelling catheters of inferior vena cava. *JAMA* 167:1606 1958.
2. Moran J M, Atwood R P and Rowe M J. A clinical and bacteriologic study of infections associated with venous cutdowns. *New Engl J Med* 272:534 1965.
3. Smith B E, Modell J H, Gaub M L and Moya F. Complications of subclavian vein catheterization. *Arch Surg* 90:778 1963.
4. Flanagan J P, Gradisar I A, Gross E J and Kelly T R. Air embolus—A lethal complication of subclavian venipuncture. *New Engl J Med* 281:488 1969.
5. Doering R B, Stremmer E A and Connolly J E. Complications of indwelling venous catheters with particular reference to catheter embolus. *Am J Surg* 111:239 1967.
6. Friedman B A and Jurgelski H C. Perforation of atrium by polyethylene CV catheter. *JAMA* 203:1131 1968.

- 7 Kline I K and Hofman W I Cardiac tamponade from CVP catheter perforation J A M A 206:1794 1968
- 8 Thomas C S Jr Carter J W and Lowder S C Pericardial tamponade from central venous catheters Arch Surg 98:217 1969
- 9 Homesley H D and Zelenik J S Hazards of central venous pressure monitoring. Pericardial tamponade Am J Obstet Gynecol 109 1216 1971

Use of indicator dilution techniques to determine patency of internal mammary artery implants

Since its introduction more than a generation ago the use of dye dilution techniques for the determination of cardiac output and the detection of shunts in the study of the circulation is now a refined and accepted technique.^{1,2} The appearance of indicator at a sampling site occurs even with very small shunts from other areas and in addition may be detected in very small concentrations.

The techniques for determining the contribution of internal mammary artery implants to myocardial perfusion and for making an assessment of the value of the operation are well documented.^{3,4} The standard technique for the determination of patency and its contribution to myocardial perfusion is internal mammary arteriography. Some question of the validity of arteriographic evidence of collateral flow has arisen and direct electromagnetic flowmeter determinations of flows have shown only a very small flow through the implant in spite of arterio-

graphic evidence of an excellent surgical result.⁵

The following study was undertaken at the time of internal mammary arteriography as a means of substantiating flow from the implant to the myocardium and in particular to determine if any collateral flow existed when the arteriographic evidence suggested an unsatisfactory result.

Methods

Six Caucasian male patients ranging in age from 46 to 57 years with predominantly anterior descending coronary artery disease were studied 16 to 24 months after a left internal mammary pedicle re-plant. Internal mammary arteriography was performed from a left brachial artery approach using a Sones or Judkins catheter and a 60 per cent Perbgrafin solution for contrast material while recording on 35 mm cineangiographic film at 60 frames per second.

Indicator dilution curves were inscribed by injecting 10 mg of indocyanine green dye into the implant and sampling from the coronary sinus by use of a No. 7 NIH catheter. Curves were inscribed in duplicate fashion following which the inter-



Fig 1 Internal mammary arteriogram showing a patent internal mammary artery with filling of the anterior descending coronary artery, a myocardial blush, and early venous phase.

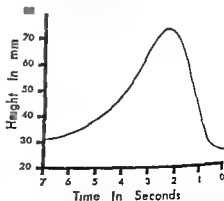


Fig 2 Indicator dilution curve typical of patients with patent internal mammary artery with filling of anterior descending coronary artery and a venous phase.

Table 1 Patients studied by means of internal mammary arteriography and dye dilution injections

Patient	Coronary lesion	Interval between surgery and study	Implant function	Appearance time	Type of curve	Clinical state
L. M.	Total obstruction middle 1/3 of ADCA*	22 months	Patent with filling of distal ADCA and venous phase	Immediate	Sharp deflection	No improvement
C. K.	Total obstruction middle 1/3 of ADCA	22 months	Patent to pericardium with collaterals into pericardium and chest wall none to myocardium	6 sec.	Small dispersed	Slight improvement
D. B.	50% obstruction ADCA at origin from LMCA and 75% obstruction at origin of CCA	23 months	Patent with filling of ADCA with venous phase	Immediate	Sharp deflection	Marked improvement
J. F.	Total obstruction proximal ADCA with distal collaterals and some disease CCA	16 months	IMA occluded halfway to myocardium	8 sec.	Small dispersed	Moderate improvement
E. B.	Total obstruction ADCA in middle 1/3	19 months	Patent with collaterals into ADCA and a venous phase	Immediate	Sharp deflection	Marked improvement
O. P.	75% obstruction ADCA at origin from LMCA	24 months	Patent into myocardium but no collaterals seen	Immediate	Small dispersed	No improvement

Abbreviations: ADCA = Anterior descending coronary artery; CCA = Circumflex coronary artery; LMCA = Left main coronary artery

internal mammary catheter tip was withdrawn just distal to the internal mammary orifice and a control curve was recorded.

Indicator-dilution curves were inscribed using a Waters densitometer, a Harvard withdrawal pump and a Texas Instrument recorder. Lag time of the sampling system was determined by the length of time necessary for blood to appear at the densitometer site.

Results

Table 1 presents a tabulation of the patients studied with the type of coronary lesion present, the interval between implantation and study, the arteriographic results, the appearance time of the indocyanine green indicator in the coronary sinus, a description of the curve and the clinical results. No correlation could be made between the clinical state and the presence or absence of patency.

The three patients with obvious filling of the anterior descending coronary artery and a venous phase in the coronary sinus (Fig. 1) had immediate

appearance of indocyanine green indicator in the coronary sinus with a sharp deflection (Fig. 2). One patient with an implant patent into the myocardium but with no evidence of collateral flow, myocardial blush or venous phase had instant appearance of indicator with a small dispersed curve (Fig. 3). Two patients with implants clearly not functioning into the myocardium had small dispersed curves delayed 6 and 8 seconds after injection of indicator with curves similar to those obtained with controls who were injected in the left subclavian artery (Fig. 4). Indicator appearance time for the controls ranged from 6 to 9 seconds.

Discussion

Indicator-dilution curves utilizing indocyanine green dye were explored in determining the patency of internal mammary artery implants. Detection techniques for this dye are very sensitive and any indicator material detected in the coronary sinus after injection into an internal mammary artery implant would signify collateral flow from the im-

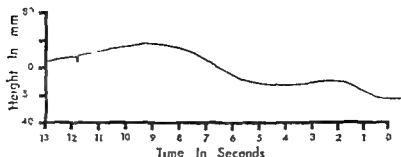


Fig. 3 Indicator dilution curve in a patient with a patent implant into the myocardium but without other evidence of collateralization

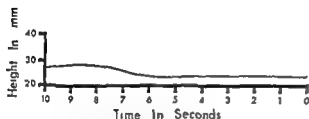


Fig. 4 Indicator dilution curve typical of patients with an occluded internal mammary artery prior to entering the myocardium

ternal mammary artery implant into the coronary circulation

Three patients with high grade arteriograms with filling of the anterior descending coronary artery and a venous phase had instant appearance of indocyanine green indicator in the coronary sinus with a sharp curve inscribed whereas two patients without evidence of patency of the internal mammary artery implant to the myocardium showed dye dilution curves consistent with systemic circulation only.

One patient showed evidence of some myocardial perfusion despite the fact that arteriographically no venous phase or collateral flow could be detected even though the implant was patent into the myocardium.

Summary

Indicator dilution indocyanine green dye curves were inscribed by injecting into the internal mammary artery and sampling from the coronary sinus in 11 patients being studied postoperatively after left internal mammary artery implants. The results were predictable from the internal mammary arteriograms: patients with obvious collateral flow on arteriography had immediate appearance of indocyanine green indicator in the coronary sinus and patients with occluded implants prior to entering the myocardium had only systemic circulation of indocyanine green. One patient with a patent vessel into the myocardium but with no evidence of collateral flow had an early but dispersed curve indicating that some myocardial perfusion was occurring

if the implant remained patent but whose arteriograms otherwise pointed to a poor result.

Grady H. Hendrix, M.D.
Associate Professor of Medicine
William C. Meloy, M.D.
Associate in Medicine

Division of Cardiology
Medical University of South Carolina
the Veterans Administration Hospital
Charleston, S.C.

REFERENCES

- 1 Hamilton W F and Remington J W Comparison of the time concentration curves in arterial blood of diffusible and nondiffusible substances when injected at a constant rate and when injected instantaneously. *Am J Physiol* 118:35 1948
- 2 Kinsman J M, Moore J W and Harrison W F Studies on the circulation—Injection method. Physical and mathematical considerations. *Am J Physiol* 89:321 1979
- 3 Taylor W J and Gorlin P Objective criteria for internal mammary artery implantation. *Ann Thorac Surg* 11:143 1967
- 4 Björk L, Cullhed I, Hallén A and Strom G Results of internal mammary artery implantation in patients with angina pectoris. *Scand J Thorac Cardiovasc Surg* 2:1 1968
- 5 Kassebaum D G, Fudkin M P and Grossi D H E Stress electrocardiography in the evaluation of surgical revascularization of the heart. *Circulation* 40:297 1969
- 6 Piccone V A, Leveen H H, Potter R T, Falk G, Manolic A and Orin E Multiple parameter evaluation of internal mammary artery implant function. *Ann Thorac Surg* 8:327 1969
- 7 Durr C H Jr, Kato Y, Scott S M, Fish P G, Nelson W M and Takaro T Internal thoracic arteriography. A questionable index of myocardial revascularization. *J Thorac Cardiovasc Surg* 59:117 1970
- 8 Durr C H Jr, Scott S M, Fish R G and Takaro T Direct blood flow studies of clinical internal thoracic arterial implants. *Circulation (Suppl II)* 64 1970

Acute elemental phosphorus poisoning in man Cardiovascular toxicity

The mortality rate after ingestion of yellow phosphorus ranges from 30 to 50 per cent.^{1,2} Most deaths occur within 36 hours reportedly secondary to peripheral vascular collapse, cardiac arrest and cardiac failure. Despite the frequency of shock in phosphorus poisoning we are unaware of any previous hemodynamic or chemical studies clarifying its pathophysiology. We have recently evaluated the cardiovascular function of a 16-year-old girl who ingested 1100 mm³ of elemental phosphorus in a suicide attempt.

Peripheral pulses were palpable at a rate of 110 per minute. Blood pressure by palpation was 60 mm. Hg systolic. The skin was cold, nail bed capillary refill was poor. Respirations were 40 per minute, the lungs were clear to auscultation. There was no palpable point of maximal impulse (PMI) heart sound were distant with an audible third heart sound and a single second heart sound. The electrocardiogram (ECG) revealed atrial fibrillation with wide slurred QRS complexes. A supine chest x-ray demonstrated diffuse cardiac enlargement and clear lung fields. One hundred per cent oxygen was administered by nasotracheal tube and the pH was raised to 7.37 with intravenous sodium bicarbonate and maintained at or above this level with periodic sodium bicarbonate infusion. Serum electrolytes after pH improvement were normal except for carbon dioxide 9.0 mEq per liter and potassium 3.0 mEq per liter. Blood sugar was 486 mg per 100 ml.

Results of the shock evaluation are summarized in Fig. 1. On 0.03 µg per kilogram per minute of isoproterenol the mean arterial pressure was 37 mm. Hg and the central venous pressure 17 mm. Hg. With discontinuation of the isoproterenol and acid-base balance improvement the mean arterial pressure rose to 47 mm. Hg. Urine production began concurrently with dopamine infusion however the mean arterial pressure fell to 35 mm. Hg. Levor-arterenol infusion at a rate of 0.13 µg per kilogram per minute increased the mean arterial pressure to 46 mm. Hg and urine production continued. Despite the low blood pressure the patient was able to answer questions and respond to command although she was lethargic. All indocyanine green dye curves revealed a late appearance time with an initial low peak followed by a higher peak and a prolonged flattened disappearance.

At 5:30 A.M. a right heart catheterization was performed to clarify the hemodynamic problem. All chambers of the heart were entered, the left atrium and left ventricle being entered through the patent foramen ovale. Pressures revealed a right atrial mean of 16 mm. Hg, a right ventricle pressure of 24/16 mm. Hg, a pulmonary artery pressure of 24/17 mm. Hg, a left atrial mean pressure of 20 mm. Hg,

a left ventricle pressure of 68/21 mm. Hg and femoral artery pressure of 74/30 mm. Hg. Hand injections of 10 ml of contrast material into each ventricle revealed a markedly generalized decrease in contractility. Indocyanine green dye curves and oxygen saturations revealed bidirectional shunting at the atrial level with a pulmonary to-systemic flow ratio of 1.5:1.0. Systemic cardiac output was calculated from the left atrial to the femoral artery dye curve after assuming a linear semilog plot of the downslope and was 5 L per minute. Calculations revealed markedly diminished systemic and pulmonary resistances of 433 and 714 dynes/cm² respectively. Clinical condition, blood pressure and urine production remained unchanged until 1:00 P.M. when 22 hours after ingesting the yellow phosphorus cardiac standstill occurred and the patient could not be resuscitated.

At postmortem examination the heart was pale, dilated and weighed 300 grams. The coronary arteries and valvular structures were unremarkable. The foramen ovale was patent. Microscopic sections revealed diffuse changes throughout the myocardium with the myocardial cells separated by interstitial edema without cellular infiltrate. The cytoplasm was vacuolated with pale linear areas.

Elemental phosphorus was administered to Sprague-Dawley rats in an effort to elicit a direct toxic biochemical effect on the myocardium. Method previously applied for the study of the toxic effect of emetine hydrochloride and certain antiarrhythmic agents were used to evaluate amino acid incorporation into soluble myocardial proteins and actomyosin.³

Depression of tritiated leucine incorporation into the pooled soluble cardiac proteins and actomyosin of the experimental animals was noted. Comparison between the specific activity of protein isolates from the control group and from experimental hearts revealed a 24 to 40 per cent inhibition of leucine incorporation produced by administration of phosphorus.

The hemodynamic data obtained from our patient strongly suggest a direct toxic effect upon the myocardium and the peripheral vessels. Vascular damage was evidenced by the extremely low systemic resistance (despite the low blood pressure) and the failure of powerful alpha adrenergic agents to increase the resistance substantially. The myocardial effect was evidenced by the elevated ventricular end diastolic pressures, the abnormal pressure tracings obtained in both ventricles, the extremely poor contractions noted on angiography and the generalized cardiac dilatation which apparently led to opening of the foramen ovale allowing bidirectional shunting at the atrial level. Additional evidence of myocardial dysfunction was the very low left ven-

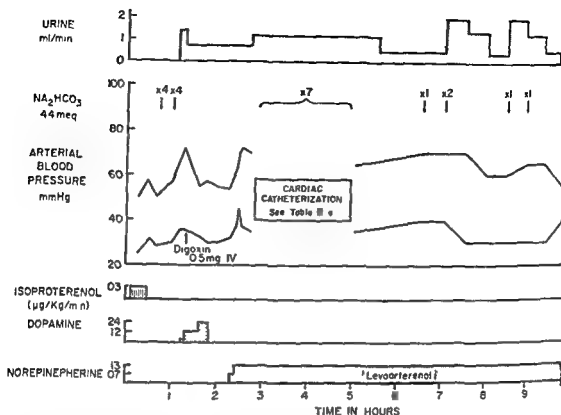


Fig 1 Hospital course of a 16 year old girl who ingested 1100 mg of elemental phosphorus nine hours prior to the recording of the initial values. Femoral artery pressures and urine flow are shown as well as the various drugs used in an attempt to correct the cardiovascular abnormalities. See text.

tricular pressure rise ($dp/dt = 588$ mm Hg per second) in the presence of a high preload.¹¹

Most toxicological references merely state that elemental phosphorus acts as a general protoplasmic poison probably in interfering with enzyme systems.¹² However, Barker and co-workers⁹ found phosphorus to depress intracellular protein synthesis in the liver but not in the pancreas or duodenum. Our data indicate a similar depression of rat myocardial protein synthesis due to acute phosphorus poisoning. Although we are unable to determine the mechanism by which phosphorus acts to inhibit amino acid incorporation into myocardial proteins, we feel that the metabolic effect demonstrated is related to the cardiac dysfunction seen in our patient.

Robert C. Talley M.D.
Joseph W. Linhart M.D.
Alphonso J. Trevino M.D.
Linda Moore B.A.
Barry W. Beller M.D.
Department of Physiology & Medicine
The University of Texas Medical School
at San Antonio
San Antonio, Texas 78229

REFERENCES

- Jacobziner H and Raybin H W. Phosphorus poisoning including two fatal case reports. *Arch. Pediatr.* 78:396, 1961.
- Diaz Rivera R S, Collazo P J, Pons E R, and Torregrosa M V. Acute phosphorus poisoning in man. A study of 56 cases. *Medicine* 29:269, 1950.
- Rubitsky H J and Myerson P M. Acute phosphorus poisoning. *Arch. Intern. Med.* 83:164, 1949.
- Beller B M. Observations on the mechanism of emetine poisoning of myocardial tissue. *Circ. Res.* 22:501, 1968.
- Beller B M and Mongillo S. Inhibition of incorporation of leucine into myocardial protein of the rat by antiarrhythmic agent. *Circ. Res.* 25:401, 1969.
- Gault J H, Ross J Jr, and Braunwald E. Contractile state of the left ventricle in man. Instantaneous tension velocity-length relation in patients with and without disease of the left ventricular myocardium. *Circ. Res.* 22:451, 1968.
- Mason D T. Usefulness and limitations of the rate of rise of intraventricular pressure (dp/dt) in the evaluation of myocardial contractility in man. *Am. J. Cardiol.* 23:516, 1969.
- Stewart C P and Stolman A. *Toxicology*. New York, 1961. Academic Press, Inc. Vol. II, p. 834.
- Barker E A, Smuckler E A, and Benditt E P. Effects of thiocetamide and yellow phosphorus poisoning on protein synthesis in vivo. *Lab. Invest.* 12:955, 1963.

Angle of traction of the papillary muscle in normal and dilated hearts A theoretic analysis of its importance in mitral valve dynamics

The left ventricular papillary muscles are important constituents of the mitral valve apparatus. During ventricular systole the papillary muscles necessarily develop tension to prevent the mitral valve from everting into the left atrium, thereby preventing regurgitation of blood from the left ventricle.¹

The force developed by the left ventricle and exerted against the mitral leaflets guarding the atrio-ventricular orifice is directly proportional to the area of the orifice. In a previous report the large force exerted against the mitral leaflets and supported by the papillary muscles in both normal and dilated hearts was described.¹ In the following discussion the importance of the changing angle of traction of the papillary muscles with respect to the efficiency of papillary muscle function as systole progresses is emphasized.

The force (F) in dynes exerted on the mitral valve leaflets is given by the formula

$$F = P \times A \times 1,333$$

where P equals ventricular pressure (mm Hg) and A equals the area (sq. cm.) of the mitral valve orifice. The force exerted on the mitral valve leaflets is supported by the papillary muscles and the annulus of the mitral valve orifice with a precision that keeps the mitral valve orifice sealed throughout systole.

From examination of many hearts at necropsy it is evident that in the relaxed state the papillary muscles normally occupy a position along the ventricular wall that is approximately one half the distance from the apex of the left ventricle to the mitral valve annulus. If for convenience one assumes the ventricle to be spherical the angle formed between the papillary muscles and the mitral valve orifice at the point of attachment of the papillary muscles to the edges of the mitral valve leaflets (angle α) during early systole is about 45° (Fig. 1). However during ventricular ejection the volume and therefore the radius of the normal size left ventricle progressively reduces markedly. Also the papillary muscles and chordae tendineae progressively migrate centripetally during systole to a position almost perpendicular to the mitral valve orifice so as to form almost a 90° angle between the mitral valve orifice and the attachments of the papillary muscles to the edges of the mitral valve leaflets (Fig. 1).

The importance of the progressive change in the angle of traction of the papillary muscles as systole progresses can be illustrated by the following theoretic considerations. If it is assumed that a normal size ventricle with a mitral valve orifice of 8 sq. cm.

contains 95 c.c. of blood at the end of diastole the force (F) exerted on the mitral valve during early systole (intraventricular pressure 80 mm Hg) would be 8.53×10^6 dynes. If one assumes that the annulus and ventricular wall support one half of the total force then each papillary muscle would have to support one fourth of the total force or 2.13×10^6 dynes. However to support this force the papillary muscle would have to provide an even greater counterforce, since its force is applied to the orifice at an angle less than 90°. Thus with an angle of traction of 45° a papillary muscle would have to develop a force of 3.01×10^6 dynes in order to exert the necessary force of 2.13×10^6 dynes on the mitral valve leaflets. Following ejection of 85 c.c. of blood and assuming an intraventricular pressure of 100 mm Hg at the end of systole and no change in the size of the mitral valve orifice of 8 sq. cm. the total force exerted on the mitral valve at the end of systole would be 10.67×10^6 dynes. However since the angle of traction is almost 90° at that time during the cardiac cycle (Fig. 1) the force required of a single papillary muscle to support its share of the force against the mitral valve would be reduced to 7.68×10^6 dynes. Thus although the intraventricular pressure and in turn total force on the mitral valve leaflets are increased at the end of systole the force required of the papillary muscles to support the mitral valve leaflets is much less because of their increased mechanical advantage due to the change in the angle of traction from 45° to almost 90° when the ventricle is contracted and essentially empty. The decrease in force or tension required of the papillary muscles occurs parabolically. Differences of plus or minus 10° from an angle of traction of 90° are of little consequence.

Unfortunately with ventricular dilatation the mechanical advantage of the papillary muscles of the normal size heart during the late phase of ventricular systole is lost. In the dilated heart the papillary muscles are displaced centrifugally and are situated relatively closer to the orifice of the mitral valve than in the normal size heart. Such a position causes the papillary muscle to have an angle of traction with the mitral valve leaflets which could approximate 30°. If such a dilated left ventricle contained 500 c.c. of blood and if the mitral valve orifice increased to 13 sq. cm. (intraventricular pressure of 80 mm Hg) the total force on the mitral

If these calculations we assume an arterial blood pressure of 100/80

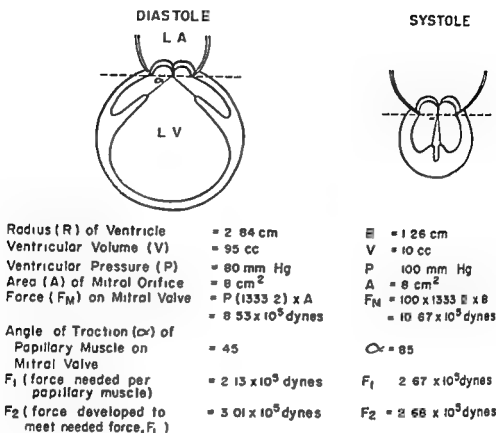


Fig. 1 Diagram showing the influence of the time course of spatial orientation of papillary muscles of the mitral valve during systole in the normal size heart on papillary muscle efficiency. Consult text for details

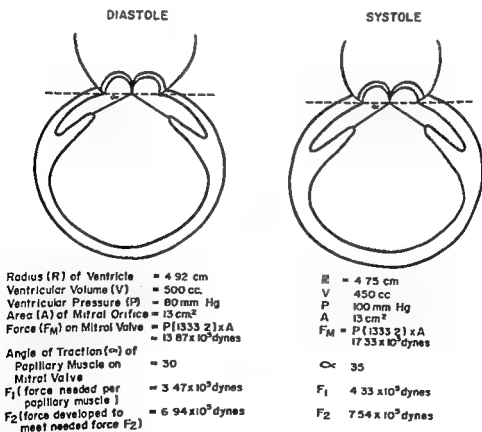


Fig. 2 Diagram showing the influence of the time course of spatial orientation of papillary muscles of the mitral valve during systole in the dilated heart on papillary muscle efficiency. Consult text for details

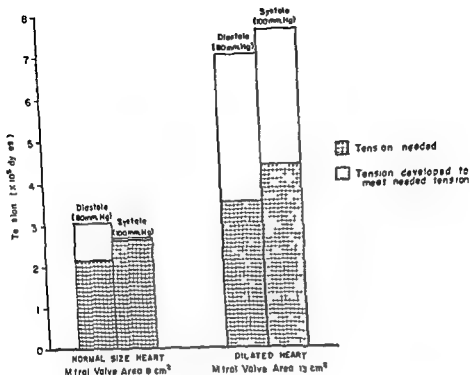


Fig. 3 The influence of heart size on force needed of and developed by a left ventricular papillary muscle

valve during early systole would be 13.87×10^5 dynes (Fig. 2) and the total force supported by each papillary muscle would be 3.47×10^5 dynes. With an angle of traction of 30° the total force required of each papillary muscle to provide an effective force of 3.47×10^5 dynes would be 6.94×10^5 dynes. Even with a stroke volume of 50 cc the radius of the dilated ventricle would decrease very little (Fig. 2) and thus the angle of traction of the papillary muscle would remain essentially unchanged perhaps increasing to 35° in some hearts. Therefore with an intraventricular pressure of 100 mm Hg at the end of systole and a mitral valve orifice of 13 sq cm the total force on the mitral valve would be 17.33×10^5 dynes and an effective force of 4.33×10^5 dynes would be required of each papillary muscle. However because the papillary muscle migrated only slightly (to a traction angle of about 35°) the force required of the papillary muscle to produce the force of 4.33×10^5 dynes would be 7.54×10^5 dynes. This is an increase in force rather than a marked decrease as seen in the normal size heart. If the angle of traction of the papillary muscle in the dilated heart could have increased to almost 90° near the end of systole as occurs in the normal size heart the force required of a single papillary muscle would have been only 4.33×10^5 dynes (Fig. 3).

Thus the mechanical advantage of the time course of spatial orientation of the normal papillary muscle of the normal size heart during systole is evident. A change in the angle that the papillary muscle forms with the mitral valve orifice from 45°

to 90° causes almost a 30 per cent reduction in the force that must be developed by the papillary muscle in spite of an increase of intraventricular pressure during systole. To realize the magnitude of the reduction in force consider that the theoretic accumulated force for a papillary muscle for one day using only peak systolic tension in calculations is 19 tons.³ Thus loss of the mechanical advantage alone of the papillary muscles in the dilated heart because of the unfavorable time course of spatial orientation of the muscles during systole would result in an increase in force developed of 57 tons per day for both papillary muscles. Because the dilated heart is a sick heart with poorly functioning myocytes its papillary muscles must perform this increased work at a time when they are not able to contract properly. Since there may be disease of the coronary circulation as well as an increase in myocardial tension the papillary muscles would be even more prone to ischemic damage.

It should be noted that the force developed by the papillary muscles is also exerted on the ventricular wall. This force aids in ventricular contraction. As the ventricles dilate the mechanical advantage normally attained by the migration of the papillary muscles during systole is lost and therefore the papillary muscles exert less effective force on the ventricular wall aiding less effectively in ventricular emptying.

Thus a changing angle of traction of the papillary muscles due to the dynamic time course of spatial orientation of these muscles during the cardiac cycle

is important in determining papillary muscle efficiency. This efficiency is considerably less in the dilated heart.

G E Burch M D

T D Giles M D

Department of Medicine

Tulane University School of Medicine

1430 Tulane Ave

New Orleans La 70112

REFERENCES

- 1 Burch G E DePasquale N P and Phillips J H The syndrome of papillary muscle dysfunction *AM HEART J* 75 399 1968
- 2 Burch G E and DePasquale N P Time course of tension in papillary muscle of heart. Theoretical considerations *JAMA* 197 01 1965

Letters to the Editor

Comment on improved maneuver for left heart catheterization

To the Editor

Described in the November 1971 issue (*AM HEART J* 87:716 1971) was an interesting and extremely practical maneuver to be used during left heart catheterization. The author stated that by having the patient hyperextend his neck and look backward it was extremely easy to enter the left ventricular chamber especially if one were using the pigtail type of catheter through the femoral artery. He also noted that this maneuver could be applied to retrograde left heart catheterization by way of the brachial artery and that even in patients with some degree of aortic stenosis this maneuver made a great difference when entering the left ventricle. This method consequently reduced the amount of x rays taken during the fluoroscopy and shortened the total time of the procedure itself. Since one of our primary goals in the cardiovascular laboratory at Deborah Hospital is to employ a catheterization procedure that will obtain the detailed data as safely and as rapidly as possible we were very much impressed with Dr. Weaver's observations. We therefore began to employ his technique in all our retrograde left heart catheterizations especially for those in which the pigtail catheter was used by way of the femoral artery. Since that beginning over 35 patients have been successfully studied by means of this technique and we felt it desirable to add our confirmation of the success of this method as well as to append a few of our own observations.

Patients examined by us fell into two groups.

Group 1 Sixty-seven patients with coronary artery disease were selectively catheterized using the retrograde right femoral arterial approach and employ in the pigtail catheter as recommended by Jenkins. In all cases the pigtail catheter was con-

sistently advanced into the root of the aorta and immediately thereafter into the left ventricular chamber. In so doing the Cook guidewire was immediately withdrawn when the pigtail catheter entered the root of the aorta. This method not only minimized the catheterization and fluoroscopy time for these patients but it also shortened the time the guidewire was within the catheter and therefore eliminated the possibility of clot formation. The only exception to this series of successful examinations was encountered in a patient with significant calcified aortic stenosis. In this patient difficulty was experienced in entering the left ventricular chamber and such an entry is not nearly so easy as the brachial arterial approach.

Group 2 All the remaining patients (eight) who were catheterized using the right brachial arterial approach also experienced a significant reduction in the time required to manipulate the Mill or Sones catheter in entering the left ventricle. It should be noted however that we again found that this technique was not as successful in patients with severe aortic stenosis. Also when comparing the retrograde approach by way of the brachial artery with the retrograde femoral arterial approach it was quite apparent that when the pigtail catheter was inserted through the femoral artery the maneuver was more successful than when the catheter was inserted through the brachial artery.

In conclusion we believe that Dr. Weaver's fortuitous discovery provides an excellent and useful method to everyone performing left heart catheterization especially when the method of entry is the retrograde transfemoral approach using the pigtail catheter.

Wladir Maranhao M.D.
Cardiology Department
Deborah Hospital
Browns Mills N. J. 08015

Book reviews

CARDIOVASCULAR REVIEW-1971 Heart Disease in India Edited by I A D Cruz Bombay 1971 Commerce Publications Division 140 pp

This interesting publication from India is primarily directed at the prevention of cardiovascular disease or its various complications and ultimate death. It is concerned with such subjects as preventive cardiology, epidemiology of heart disease in Northern India, the normal electrocardiogram and vectorcardiogram, cardiomyopathies and cor pulmonale in India. Most of the papers contained in this volume will interest cardiologists.

PROSTHETIC REPLACEMENT OF THE AORTIC VALVE By Lester K. Sturtevant et al. Springfield Ill 1972 Charles C Thomas Publisher 217 pp Price \$18.00

This is a good book devoted to an important clinical problem. The authors have included hemodynamic as well as surgical and clinical principles in their presentations; they not only discuss the structure and function of the normal and diseased aortic valve but also the prosthesis used. Hydraulic and hemodynamic principles are nicely presented in simple diagrams. Herling and histopathology as well as the clinical and surgical aspects are clearly discussed. This volume should interest cardiologists, cardiac surgeons and students at all levels of training.

BIOLOGICAL TISSUE IN HEART VALVE REPLACEMENT Edited by M I Ionescu MD, D N Ross BSc MB ChB, FRCS and G H Wooler TD MD MA FRCS London 1972 Butterworth & Co 925 pp Price \$75.00

This is a comprehensive review of the many problems related to prosthetic cardiac valves. The contributors are mainly surgeons and the orientation is therefore from the surgical viewpoint. The 37 chapters are concerned with the present status of prosthetic cardiac valves, experimental background of biological tissue in valve replacement, clinical applications, heterografts, autologous tissue, valve transplantation and reconstruction in congenital heart disease and morphologic changes in the transplanted valves. The many contributors are experts in their respective fields.

The relatively brief chapters are all directed to the practical clinical aspects of prosthetic valves. Illustrations and text are clearly presented. This is a very good review of the problems related to valve replacement in man but it is unfortunately rather expensive. Those who can afford it will find this volume very useful.

PATHOPHYSIOLOGY AND DIFFERENTIAL DIAGNOSIS OF CARDIOVASCULAR DISEASE Edited by Charles A. Friedberg MD and Ephraim Donoso MD New York and London 1971 Grune & Stratton L 336 pp Price \$15.00

Periodically papers which have appeared in the journal *Progress in Cardiovascular Disease* are bound into a single book. This is another such volume and those who subscribe to the journal already have copies of these papers; nevertheless, many of these physicians would no doubt like to have the papers collectively bound. Some of the pathophysiologic problems included in this volume are related to chest pain, pulmonary edema, syncope, cyanosis, murmurs, cardiomyopathies, acute pericarditis, hypertension, and dissecting aneurysms. The 16 papers are independently oriented—i.e. this is not a text book or monograph but a collection of papers. Such books do have a useful place in our general and private medical libraries.

ELECTROSTIMULATION OF THE CAROTID SINUS NERVE IN ANGINA PECTORIS By A J Dunning Am J Med 1971 Excerpta Medica 104 pp Price \$8.75

This brief monograph summarizes very nicely the use of electrostimulation of the carotid sinus nerves in the management of angina pectoris. Dunning describes his own experience with the method and finds it to be useful in selected cases unresponsive to conventional procedures. The booklet is divided into four parts: namely, carotid sinus reflex, effects of stimulation of the carotid sinus nerve, clinical results, and circulatory and respiratory effects of carotid sinus nerve. This book is a good single source of discussion of carotid sinus nerve electrostimulation for angina pectoris.

Books received

THE BIOLOGICAL IMPERATIVES—Health Politics and Human Survival By Allan Chase New York Chicago and San Francisco 1971 Holt Rinehart & Winston Inc 399 pages Price \$11.95

MANUAL OF PREOPERATIVE AND POSTOPERATIVE CARE Ed 2 Edited by John M Kinney M D Richard H Egdahl M D and George D Zuidema M D Philadelphia 1971 W B Saunders Company 644 pages Price \$11.00

MEDICAL INTERVIEWING—A Programmed Manual Ed 2 By Robert E Froelich M D and F Marian Bishop Ph D St Louis 1972 The C V Mosby Company 131 pages Price \$5.00

ORGAN PHYSIOLOGY—STRUCTURE AND FUNCTION OF THE CARDIOVASCULAR SYSTEM By Robert F Rushmer M D Derived from CARDIOVASCULAR DYNAMICS Ed 3 Philadelphia 1972 W B Saunders Company 249 pages

THE PATHOPHYSIOLOGY AND TREATMENT OF DROWNING AND NEAR DROWNING By Jerome H Modell M D Springfield Ill 1971 Charles C Thomas Publisher 119 pages Price \$9.50

TRANSLATION OF DE SUBITANEIS MORTIBUS (ON SUDDEN DEATHS) By Dr Paul Dudley White and Professor Alfred V Boursy Jamaica 1971 St John's University Press 212 pages

LASERS IN MEDICINE By Leon Goldman M D and R. James Rockwell Jr New York London and

Paris 1971 Gordon and Breach Science Publishers Inc 385 pages.

VECTOCARDIOGRAPHY 2 Proceedings of the XI International Symposium on Vectorcardiography held in New York May 13-17 1970 sponsored by the Long Island Jewish Medical Center Edited by I Hoffman H J Hamby and E Glassman Philadelphia and Toronto 1971 J B Lippincott Company 706 pages Price \$39.50

PHYSIOLOGICAL BASIS OF REHABILITATION MEDICINE Edited by John A Downey M D and Robert C Darling M D Philadelphia 1971 W B Saunders Company 445 pages

1971 YEAR BOOK OF SURGERY Edited by Seymour I Schwartz M D John S Najarian M D Erle E. Peacock Jr M D G Tom Shires M D William Silen M D and Frank C Spenser M D Chicago 1971 Year Book Medical Publishers Inc 516 pages. Price \$14.00

CARE OF THE SURGICAL CARDIOPULMONARY PATIENT Edited by William E. Neville M D Chicago 1971 Year Book Medical Publishers Inc 313 pages. Price \$17.50

ADVANCES IN SURGERY Vol 5 Edited by Claude E. Welch and James D Hardy Chicago 1971 Year Book Medical Publishers Inc 334 pages Price \$18.50

Announcements

Fondation de Physiopathologie Professeur Lucien Dautrebande prize

The Fondation de Physiopathologie Professeur Lucien Dautrebande will award during the year 1973 an international prize of approximately 500 000 Belgian francs (\$10 000 U.S.) for the outstanding study submitted on human or animal physiopathology. It is preferable that this study shall have therapeutic implications. For further information regarding this prize please write to the office of the Foundation 35 Chaussée de Liège 5200 HUY, Belgium.

Two Cardiovascular Nursing Courses

The Cardiovascular Education Program Nashville Tenn. announces two courses in cardiovascular nursing for nurses. The first for Licensed Practical Nurses will be a four week course running from July 21 through August 25 1972. The second for Registered Nurses will be an eight week course of classroom experiences and independent study running from October 2 through November 24 1972.

For further information about these courses please contact the Education Director The Cardiovascular Education Program 1107 Eighteenth Ave. South Nashville Tenn. 37203 or call 615 327-4031.

Editorial

The problems of deep vein thrombosis

N L Brewse MD FRCS
London England

Deep vein thrombosis has always been a serious complication of medical illness, surgical operations and childbirth but whereas we have mastered other difficulties such as infection, blood and fluid losses and the complications of anesthesia we have made little headway in preventing deep vein thrombosis so that its relative incidence and importance have steadily increased.

More than 100 years ago Virchow¹ described the formation of thrombus in the cusps of the peripheral veins, its propagation and then its fragmentation to produce a pulmonary embolus. The early pathologists also noted that deep vein thrombosis and pulmonary embolism were very common findings in the absence of clinical signs, but the real significance of their work was not appreciated.

The modern clinician can approach the problem in two ways. First, he can attempt to prevent deep vein thrombosis altogether, this is the ideal to which we all strive. Second, he can try to diagnose the peripheral thrombosis as early as possible before a pulmonary embolism occurs so that he can treat it more easily and effectively.

Methods of prophylaxis depend on a knowledge of the etiology of deep vein thrombosis. We have made little progress in this sphere since Virchow's original hypotheses on the causes of intravascular

thrombosis—changes in the blood, changes in the vessel wall and changes in the rate of blood flow. The changes in the blood that are associated with thrombosis are not yet clearly defined and those that are known are difficult to alter. The administration of anticoagulants will often prevent thrombosis but this is a shotgun approach in an attempt to miss none of a multitude of possible etiological factors. We do not know if the integrity and function of the vein wall changes during illness nor are we aware of the importance of minor damage to the intima so that this second factor of the triad cannot yet be altered. The only factor of Virchow's triad that can be altered with ease is the rate of venous blood flow. Surgeons in particular have tried to increase the rate of blood flow in the limbs following surgery in an attempt to reduce the incidence of postoperative deep vein thrombosis. Unfortunately, simple measures such as early ambulation,² elevation of the foot of the bed³ and elastic stockings^{4,5} have not been convincingly proved efficacious for two reasons. First, most of the studies published before 1960 were performed without careful control, second, not until the last five years have we had an easy and reliable method of diagnosing deep vein thrombosis in all patients. The latter problem has been solved with the advent of the I¹²⁵ fibrinogen uptake test^{6,7} and we can

From the Department of Surgery, St. Thomas and St. Bartholomew's Hospitals, London, E. England.

Received for publication June 11, 1971.

Reprint requests to Dr. N. L. Brewse, Department of Surgery, St. Thomas and St. Bartholomew's Hospitals, Medical School, London, S.E. 1, England.

now detect 95 per cent of all postoperative deep vein thrombi immediately as they appear; however, the thrombi that we detect by this test are not all clinically significant. We are currently working on the assumption that any prophylaxis which prohibits the development of the fibrinogen detectable thrombus ought to have some effect on the overall incidence of thrombosis and pulmonary embolism but this assumption may turn out to be false.

The methods of prophylaxis that have been studied with the 125 I fibrinogen uptake test are elastic stockings,⁵ general measures such as early ambulation, physiotherapy, and elastic stockings combined,¹⁰ elevation of the legs,¹¹ and stimulation of the calf muscles with an electrical current.¹² Elastic stockings have been shown to be of no value, probably because the pressure exerted by a stocking is so critical that it is likely to be either too loose and so ineffective, or too tight and so reduce the rate of blood flow.¹³ Even when a stocking is applied at the optimum pressure the increase in venous volume flow is only in the region of 15 to 20 per cent so it is not surprising that no one has shown elastic stockings to be of value. The effect of a combination of the routine methods of prophylaxis such as early ambulation, physiotherapy, elevation of the foot of the bed, and so on has been studied in an unselected series of patients without matched or concurrent controls.¹⁴ This study failed to show any benefit from these measures although when the patients were divided into different age groups the treated elderly patients did have a lower incidence of thrombosis.

Electrical stimulation of the calf muscles was suggested and was studied by Doran and White in 1967¹² and the method has recently been reassessed using 125 I fibrinogen.¹⁵ Stimulation reduces the incidence of postoperative fibrinogen detectable thrombi by approximately 60 per cent but the method has not been widely accepted because of the practical inconvenience of applying the electrodes and because others have declared without producing objective evidence that it does not work. However the critics of the method have not used the same form of stimulation so their studies are not strictly comparable

to those of Doran and colleagues or of Browse and Negus and it may be that different methods of stimulation have different effects upon calf blood flow and metabolism.

A square wave electrical stimulus every two seconds sufficient to cause a firm dorsiflexion of the foot doubles the velocity of venous return and the arterial inflow to the calf. Some investigators¹⁶ have suggested increasing venous velocity flow by passive flexion of the foot or by rhythmic compression of the leg with a 'pneumatic' stocking.¹⁴ Both of these methods are being currently investigated and the preliminary results of passive flexion show an effect similar to that of electrical stimulation.¹⁵

The combined results of all these studies will be of interest for if the passive methods do reduce deep vein thrombosis then at last we will have confirmed that venous stasis plays an important role in the etiology of thrombosis. The good response to electrical stimulation does not by itself prove that venous stasis is important since active contraction of the muscles is associated with many other changes in the metabolism and blood flow of the muscle.

The progress of this form of research suggests that in a few years we may be able to prevent development of deep vein thrombosis in many patients after surgical operations; however no method is likely to be wholly effective and none of the methods so far described is easily applicable to sick people at home or to medical patients in the hospital. For these and for the high risk surgical patients we still have to rely on anticoagulants for this is the only universally applicable form of prophylaxis which has been undeniably shown to reduce the incidence of fatal pulmonary embolism^{17, 18} in spite of the fact that it does not reduce the incidence of 125 I fibrinogen detectable thrombi.¹⁵

The alternative to prevention is early diagnosis and treatment. Since the development of the fibrinogen uptake test and the ultrasound flow detector and the resurgence of interest in phlebography we have had three excellent and complementary methods of diagnosis. It is not practical to screen all patients with these tests but they can be used on those at risk, namely upon those with a previous history of pul-

monary embolism and deep vein thrombosis also upon the very old and upon those patients having cachexia, carcinomas and those with serious medical diseases.

The simplest and quickest screening technique is to examine the major veins from the knee to the beginning of the venous arch with the ultrasound flow detector.^{20, 21} This will not detect small thrombi developing in the calf or in the thigh muscles but such thrombi are unlikely to produce a massive pulmonary embolism. The type of thrombus the ultrasound technique detects is the large and dangerous variety and this type must be immediately studied by phlebography and treated. It is better to detect the thrombus when it is small and insignificant with the fibrinogen uptake test but for logistic reasons it is not practical to use this test on all patients. However the use of this test should be encouraged because if the thrombus can be detected before the appearance of clinical signs the clinician can then follow the growth or regression of the thrombus over a period of approximately five days. Without this additional facility the test would be of doubtful value because the majority of the small thrombi that it detects after an operation are symptomless unimportant and regress spontaneously. By making daily examination the 20 per cent of thrombi that propagate²² can be detected and treated as these are the thrombi that are likely to give rise to pulmonary emboli and leg symptoms. Although the test works best if the fibrinogen is given before the thrombosis begins it is almost as reliable when the fibrinogen is given after the thrombus has formed making it possible to detect and follow established thrombi in medical cases in a similar manner.²³

The purpose of treatment of a small thrombus discovered in its early stages of development is to prevent its getting any bigger. This can usually be achieved with anticoagulants: most physicians use heparin followed by warfarin. The treatment of a large thrombus which might become a fatal pulmonary embolus or cause the femoral vein occlusion must be more active and in this context treatment must be a form of therapy which actually removes the thrombus or at second best locks it in the legs. There are two ways of removing a

thrombus—pharmacologically with thrombolytic drugs (streptokinase or urokinase) or surgically. Both forms of treatment should be available because although equally effective in ideal circumstances there are usually good reasons in any particular patient to contraindicate the use of one or the other. For example streptokinase is contraindicated in the early post-operative phase and thrombectomy cannot remove thrombi in the lower leg further more both methods fail when the thrombus is aging and adherent.

The use of anticoagulants alone in a situation where phlebography has shown a large loose thrombus likely to produce a pulmonary embolus can only be justified if the physician is certain that the thrombus is not likely to fragment and embolize. At the moment we do not know how to decide this problem and all clinicians have seen cases of pulmonary embolism occurring in the presence of adequate anticoagulation. In these circumstances if streptokinase or thrombectomy are contraindicated up stream vein ligation or plication will prevent further embolism without a major increase in the incidence of late sequelae in the legs.²⁴

It cannot be too strongly emphasized that all methods of treatment must be based on an exact anatomical knowledge of the site and nature of the thrombus information which can only be obtained by phlebography.

In summary we have made some progress over the past five years in prophylaxis and diagnosis of deep vein thrombosis but we have had less success in improving our methods of treatment. The new methods of diagnosis should allow us to treat patients earlier although it has yet to be proved that this will reduce embolism or decrease late sequelae. There are very many years of hard work between today's empirical approach and an effective method of prophylaxis for all patients or a treatment which will safely remove all thrombi and leave normal veins.

REFERENCES

- 1 Vrethow R. *Brit J Exp Pathol Physiol* 21: 181-6
- 2 Nelson H. Early ambulation following section of anterior abdominal wall. *Analysis* of 426

- personally conducted cases *Arch Surg* 19 1 1944
- 1 Pearson A The prevention of pulmonary embolism *Br Med J* 1:613 1954
 - 4 Wilkins R W Mixer G Jr Stanton J K and Litter J Elastic stockings in prevention of pulmonary embolism Preliminary report *N Engl J Med* 246:360 1952
 - 5 Markin G S A clinical trial of tubigrip to prevent deep venous thrombosis *Br J Surg* 56:373 1969
 - 6 Hobb J T and Davie J W Detection of venous thrombosis with ¹²⁵I labelled fibrinogen in the rabbit *Lancet* 2:134 1960
 - 7 Atkin P and Hawkins L A Detection of venous thrombosis in the legs *Lancet* 2 1217 1965
 - 8 Fine C Kikkar V V and Clarke M B The detection of venous thrombosis of the legs using ¹²⁵I labelled fibrinogen *Br J Surg* 55:747 1968
 - 9 Nequ D Pinto D J Le Que ne I I Brown N and Chapman M ¹²⁵I labelled fibrinogen in the diagnosis of deep vein thrombosis and its correlation with phlebography *Br J Surg* 55:835 1968
 - 10 Fine C Kikkar V V and Clarke M B Postoperative deep vein thrombosis: Effect of intravenous prophylaxis *Lancet* 1:477 1970
 - 11 Brouse N I (In pre s)
 - 12 Brouse N I and Nequ D Prevention of postoperative leg vein thrombosis by electrical muscle stimulation: An evaluation with ¹²⁵I labelled fibrinogen *Br Med J* 3 615 1970
 - 13 Sibrio M Roberts V C and Pichard J B Effect of externally applied pressure on femoral vein blood flow *Br Med J* 1:719 1970
 - 14 Doran I S and White H M A demonstration that the risk of postoperative deep venous thrombosis is reduced by stimulating the calf muscles electrically during the operation *Br J Surg* 54 686 1967
 - 15 Sibrio M Roberts V C and Cotton L T Prevention of early postoperative deep vein thrombosis by passive exercise of leg during surgery *Br Med J* 3 387 1971
 - 16 Calnan J S Paine J J and Mills C J Pneumatic intermittent compression for stimulating calf muscle pump *Lancet* 2 94 1970
 - 17 Barritt D W and Jordan S C Antecubital drug in the treatment of pulmonary embolism: A controlled trial *Lancet* 1:560 1960
 - 18 Scovitt S and Gallagher V G Prevention of venous thrombosis and pulmonary embolism in injured patients: A trial of anticoagulant prophylaxis with phenindione in middle-aged and elderly patients with fractured necks of femur *Lancet* 2:931 1959
 - 19 Pinto D J Controlled trial of an anticoagulant (warfarin sodium) in the prevention of venous thrombosis following hip surgery *Br J Surg* 57 349 1970
 - 20 Strandnes D L Schultz R D Sumner D S and Kushmerck H J Ultrasonic Doppler detection: A useful technique in the evaluation of peripheral vascular disease *Am J Surg* 113 311 1967
 - 21 Ivan D S and Cockett I B Diagnosis of deep vein thrombosis with an ultrasonic Doppler technique *Br Med J* 2 807 1969
 - 22 Kikkar V V Howe C T Flann C A and Clarke M B Natural history of postoperative deep vein thrombosis *Lancet* 2 730 1969
 - 23 Brouse N I Croft D and Thom M L (In pre s)
 - 24 Brouse N I Thomas M I Solin M J and Young V T Prevention of recurrent pulmonary embolism *Br Med J* 3 387 1969

Racial variations in the childhood electrocardiogram Preliminary observations

Daniel A. Masica M.D.

Barry J. Maron M.D.*

L. Jerome Krovetz M.D. Ph.D.**
Baltimore Md

Several standards for the normal electrocardiogram (ECG) in children are available¹⁻⁴ which take into consideration age differences but generally ignore other variables which may affect the ECG such as race, sex, and body build. Racial differences in the ST segment and T wave precordial voltages and QRS duration in the ECG of adult American Negroes and Caucasians have been suggested.⁵⁻⁸ It has been our clinical impression that normal Negro children often have increased precordial voltage suggesting left ventricular hypertrophy. This study was therefore undertaken to obtain preliminary comparative information on the ECG of normal American Negro and Caucasian children.

Materials and methods

Standard 12 lead ECGs were obtained on 64 normal male children (33 Negro and 31 Caucasian) 5 to 7 years of age. ECGs were recorded at 50 mm per second on an Electronics for Medicine DR 8 Research photographic recorder. A photographic ECG recorder was used because of its generally superior frequency response compared with direct writer instruments⁹⁻¹⁰ and

also because it enabled us to compare our results with those of Ziegler.¹ The frequency response for this recorder exceeds the minimum standards established by the American Heart Association¹¹ (see Fig. 1).

The 33 Negro children were selected consecutively over a six week period from the Johns Hopkins Hospital Comprehensive Child Care Clinic (CCCC). All children in the CCCC reside in one of eight census tracts of inner city Baltimore within a two mile radius of Johns Hopkins Hospital. These children are from families of low socioeconomic status. Caucasian subjects were chosen from St. Vincent's Orphanage in Baltimore County and the Johns Hopkins Hospital University Health Center and represented a higher socioeconomic group than the Negro subjects. Children from the University Health Center were dependents of Hospital house staff or University graduate students.

All subjects had a comprehensive cardiovascular examination including cuff blood pressure determination by at least two observers. Height, weight, and chest circumference were routinely recorded. Hematocrit was obtained on the day of exami-

From the Hill-B-T Long Children's Cardiac Clinic, The Johns Hopkins Hospital, Baltimore, Md.

Received for publication Sept. 22, 1971.

Reprints request to Dr. Barry J. Maron, Department of Pediatrics, Johns Hopkins Hospital, Baltimore, Md. 21205.

*This work was completed while Dr. Maron was a Heart Association of Maryland Research Fellow.

**Dr. Krovetz is the recipient of a Research Career Development Award (5-K3 HE-0061-07).

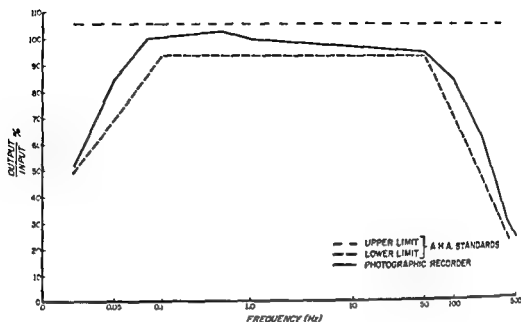


Fig. 1 Frequency response of photographic ECC recorder used in this study compared with American Heart Association minimum standard

Table 1 Physical measurements in 64 normal 5 to 7 year old male subjects

Variables	Caucasian	Negro
No. of patients	31	33
Age (yr) (mean \pm S D)	6.13 \pm 0.91	6.47 \pm 0.82
Range	5.00—7.92	5.17—7.97
Ht (cm) (mean \pm S D)	116.5 \pm 7.12	117.7 \pm 7.36
Range	105—129	101—130
Wt (kg) (mean \pm S D)	21.9 \pm 3.72	22.4 \pm 4.05
Range	17.6—32.0	15.6—37.3
Chest circumference (cm) (mean \pm S D)	59.6 \pm 2.99	58.7 \pm 3.55
Range	55.7—67.3	50.9—70.5

nation. Children with fever (exceeding 101 degrees), sickle cell anemia, hypertension, heart disease, renal disease, or other chronic illnesses were excluded from the study. All ECGs were interpreted independently by two investigators. Seven children with ECG evidence of left ventricular hypertrophy (LVH) were recalled for chest radiographs and Frank vectorcardiograms (VCG). Data from the two patient groups were compared with Student's *t* test.

Results

Comparison of physical measurements are summarized in Table 1. There was no statistically significant difference between

the Caucasian and Negro groups in height, weight, or chest circumference. Mean ages of subjects in the two groups were similar. Hematocrit values for Negroes and Caucasians were comparable, and in no instance did they deviate from accepted normal values.¹²

Standard and unipolar leads. The QRS duration was significantly shorter in the Negro group ($p < 0.001$). QRS interval in Negro subjects ranged from 0.04 to 0.08 seconds with a mean value of 0.06 second, and in Caucasian subjects the range was from 0.06 to 0.10 seconds with a mean value of 0.08 seconds.

There were no statistically significant

Table II Precordial voltages in 64 normal 5 to 7 year old male subjects

Variables	Caucasian	Negro	p value
No. of patients	31	33	
R_{V1} (mm) (mean \pm S.D.)	7.5 \pm 7.67	9.2 \pm 4.97	<0.10
Range	3.0-13.0	3.0-21.0	
S_1 (mm) (mean \pm S.D.)	9.9 \pm 3.71	14.2 \pm 6.29	<0.005
Range	3.0-17.0	3.0-33.0	
R_{V2} (mm) (mean \pm S.D.)	15.9 \pm 4.66	18.6 \pm 6.35	<0.10
Range	4.0-28.0	7.0-34.0	
S_2 (mm) (mean \pm S.D.)	17.5 \pm 5.98	19.0 \pm 5.68	<0.10
Range	4.0-37.0	9.0-34.0	
R_3 (mm) (mean \pm S.D.)	24.4 \pm 6.23	26.6 \pm 7.37	<0.30
Range	14.0-47.0	16.0-44.0	
R_{V4} (mm) (mean \pm S.D.)	15.8 \pm 4.27	17.4 \pm 5.07	<0.20
Range	10.0-26.0	8.0-30.0	

differences between the two groups in PR or QT interval amplitude and duration of P wave or R wave voltage in the standard and unipolar leads. Mean frontal QRS axis was $+60$ degrees for Negro subjects and $+80$ degrees for Caucasian subjects. One Caucasian subject had left axis deviation of -36 degrees.

Precordial leads. Data on precordial lead voltages for the two groups are summarized in Table II. The depth of the S wave in V_1 was significantly greater in Negro subjects ($p < 0.005$). The S_{V1} measured from 3 mm to 33 mm with a mean value of 14.2 mm in the Negro group and 3 mm to 17 mm with a mean value of 9.9 in the Caucasian group. Rank order of amplitudes for S_{V1} for both groups showed that the highest ranking 12 subjects were Negro. S_{V1} amplitudes approximated a normal curve in both groups with the Negroes having a wider range and a greater dispersion.

There were no statistically significant differences between the two groups for R or S wave voltages in Leads V_2 through V_4 and for R wave voltage in Lead V_1 . However a consistent tendency toward greater precordial voltages is noted in Negro subjects. Mean voltages are greater in Negroes than in Caucasians for R_{V1} , R_{V2} , S_{V2} , P_{V3} and R_{V4} although the differences are not statistically significant. ST elevation or depression was not observed. One Cau-

casian subject showed J point elevation of 2.5 mm in the left chest leads.

Abnormal precordial voltages suggesting LHH were present in 7 subjects. LCC, VCC and x-ray data for this group are summarized in Table III.

Discussion

Reports of racial variation in the ECG of adult American Negroes include ST T changes, increased voltages and shortened QRS duration.¹⁻³ Thomas, Harrison and Lister² in a study of 370 healthy young Negro adults found ST segment elevation in the left precordial leads in 27 per cent of male subjects. Gottschalk and Craig¹ in a comparative study of Negroes and Caucasians found a higher incidence of ST segment elevation among Negroes. Wasserburger³ called attention to persistence of the juvenile pattern of T wave inversion in right chest leads in healthy adult male Negroes. However other investigators have disputed this finding.¹¹ Lipberger and co-workers⁷ in an analysis of the orthogonal ECG and VCG in 518 normal men found Negroes to have significantly shorter QRS intervals and greater maximal spatial vectors. ST T changes or increased QRS voltage have also been reported in the South African Negro,^{14, 16} Ceylonese,¹⁷ West Indians,¹⁸ Peruvians,¹⁹ Japanese²⁰ and populations in India.²¹

Table III Seven subjects with electrocardiographic diagnosis of left ventricular hypertrophy

Subject	Race	Age (yrs)	ECG				Overall rotation		
			Precordial voltage (mm)						
			S ₁	R _s	R _a	Q _s	Frontal	Horizontal	Vertical
C M	Negro	7 04	24	44	30	4	Figure of eight	CCW	CCW
G J	Negro	7 02	16	42	29	2	Figure of eight	CCW	CCW
J G	Caucasian	6 00	14	42	26	5	CW	CCW	CCW
J W	Caucasian	5 45	15	38	24	3	CW	CCW	CCW
T G	Negro	6 77	8	40	24	2	CW	CCW	CCW
M M	Negro	5 25	33	17	14	2	CW	CCW	CCW
H B	Negro	7 37	24	19	16	2	CW	CCW	CCW

Maximal spatial vector in the left (Normal = 21 to 20 mv)

†Sum of maximal spatial vectors to the left (LMSV) + 10 msec

‡Sum of maximal left and posterior vectors (Normal = < 3.5 mv)

Our findings indicate that American Negro male children have significantly deeper S₁ than do Caucasian controls. African investigators have made similar observations regarding racial differences in the ECG. Walker and Walker¹⁶ found greater precordial voltages (maximum R + S) in South African Bantu male children as compared to Caucasians and Sutin and Schrire¹⁵ reported S₁ to be greater in Bantu newborns than whites. Aschcroft and associates²² reported S₁ to be significantly greater in African than in Indian counterparts in Guyana.

Possible factors in the genesis of these racial variations in the ECG include body habitus composition and nutrition. Correlation between ECG parameters and body build has been reported in adults^{7, 22, 4} but is disputed in children.² Negro subjects in this study differed slightly in body build compared with Caucasian subjects as indicated by the greater mean weight and height and smaller mean chest circumference for the Negro group. However there were no apparent relationships between precordial voltages and height, weight or chest circumference in either group. Those

patients with abnormal QRS voltage (Table III) did not show any significant difference in body build.

Differences in body composition as a source of variation in the ECG have been suggested by other investigators.⁷ Experimental work indicates Caucasian male children have proportionately more body fat than Negro controls.⁶ While it is often suggested that obesity is responsible for decreased precordial voltages,⁷ experimental evidence for this is lacking. Individual variation in torso dimension or skin resistivity²⁷ have also been suggested as possible explanations for tall precordial potentials.

Chronic severe anemia has been incriminated as a cause of tall precordial voltage in the left chest leads presumably due to the high output state.⁸ In the present study there were no anemic subjects and no apparent relationship between hematocrit and ECG voltages.

Our findings of shorter QRS duration in Negro male children agree with the observations of Pipberger and associates⁷ who found the mean QRS duration in normal adult male Negroes to be 7 msec less than

Direction initial forces	A smuth (degrees)	ECG spatial scalar measurements			Chest x ray
		LVSA (mm)	Sum of LUSV (m)	Sum of max LUSV	(CTR)
t. Right Inf	+70	2.75	4.36	5.13	0.53
t. Inf	-34	1.75	3.15	2.54	0.56
t. Right Inf	-70	1.57	3.15	2.83	0.40
st. Inf	-42	1.70	3.47	3.47	0.53
st. Right Inf	+37	1.35	3.73	2.14	0.41
st. Right	-18	1.57	3.60	3.76	0.5
st. Right Inf	-45	1.47	3.45	2.81	0.45

31 (1)

in adult male Caucasians. These findings suggest that the diagnosis of conduction defects in Negroes may be obscured by racial variation. Racial differences in the anatomy of the conducting system is an intriguing but undocumented explanation for these discrepancies.

The ECC diagnosis of LVH in children is commonly based on the magnitude of precordial voltage. Accepted normal standards employed are generally those of Ziegler.¹ For the purposes of this study, the diagnosis of LVH by magnitude of precordial voltage was defined as R_{14} or S_{14} which exceeded two standard deviations from the mean.² These values taken from Cassis and Ziegler's tables²³ were $S_{V1} = 24$ mm and $R_{V4} = 21$ mm. Because of the poor reliability of combined criteria for ventricular hypertrophy² (e.g. $S_{V1} + R_{V4}$) in children, no attempt was made to use such criteria as parameters of LVH in this study.

Seven subjects had precordial voltage which exceeded normal accepted ECC standards (Table III). Five of these children were Negro and two were Caucasian. All subjects in the group were asymptomatic

and had no evidence of cardiovascular disease.

A VECG was performed on these children to determine whether increased precordial potentials represented abnormal posterior forces indicative of LVH. Spatial and loop analysis of VECGs were compared with available normal values for children.²⁴

Two of the 7 (J W and G J) had radiographic evidence of mild cardiac enlargement with prominent left ventricular contours (Fig. 2 A and B). Spatial measurements of the VECGs in these subjects were normal although the horizontal loop of subject J W is oriented posteriorly (Fig. 3A) with a maximal spatial vector at the upper limits of normal. Two other subjects (C M and M M) had borderline cardiac enlargement. The VECG of C M suggests LVH with increased maximal spatial vector and summed maximal left and posterior vectors (Fig. 3B). Three children (J G, T G and K G) are examples of LVH determined by magnitude of precordial voltage only. Two of these children had only deep S waves in the right precordial leads and one demonstrated tall left chest potentials. VECGs and chest x rays were



Fig. 2 A and B Posteroanterior chest radiograph in two subjects with left ventricular hypertrophy determined by magnitude of precordial voltage. A Subject J W. Cardiothoracic ratio is 0.53 and prominence of left ventricular contour is present. B Subject C M. Borderline cardiac enlargement is shown with cardiothoracic ratio 0.53.

within normal limits in these three patients.

There are several possible explanations for the diagnosis of LVH determined by the magnitude of precordial voltage encountered in the seven subjects in this study. First accepted normal standards for the childhood ECG may be too restricted. Certainly the tables of Ziegler¹ which are generally regarded as the basis of the normal childhood ECG utilized a relatively small number of subjects and may not provide a representative sample. For example, the normal limits for S_{V1} in 5- to 9-year-old children is based on only 44 subjects.

It is difficult to fully explain the findings in the two patients (J W and G J) with ECG VCG, and radiographic evidence suggesting LVH. Perhaps these subjects represent an early form of endomyocardial disease or idiopathic hypertrophic subaortic stenosis since the absence of any cardiovascular signs or symptoms generally excludes other forms of congenital or acquired heart disease. Since all 7 subjects with LVH determined by the magnitude of precordial voltage are asymptomatic and without signs of cardiovascular disease, it is perhaps most reasonable to regard them as normal variants. Further clinical studies

are being conducted on a larger group of children with LVH determined by voltage to clarify the factors responsible for this ECG abnormality.

The purpose of this pilot study was to determine whether ECG differences between Negro and Caucasian children could be documented. Five to seven-year-old male children were selected for study in order to provide as homogeneous a population as possible and also because of our clinical impression that this group of children was most likely to yield positive results. However, it is quite possible that other studies utilizing different age groups, female children, or large populations may offer further substantiation of ECG differences between Negro and Caucasian American children.

Summary

A comparative ECG study of 64 normal male Negro and Caucasian children revealed deeper S_{V1} and shorter QRS duration in Negro subjects. These findings suggest that normal ECG standards for children may require adjustment for race. The clinical features of seven subjects with left ventricular hypertrophy (LVH) determined by voltage are discussed.

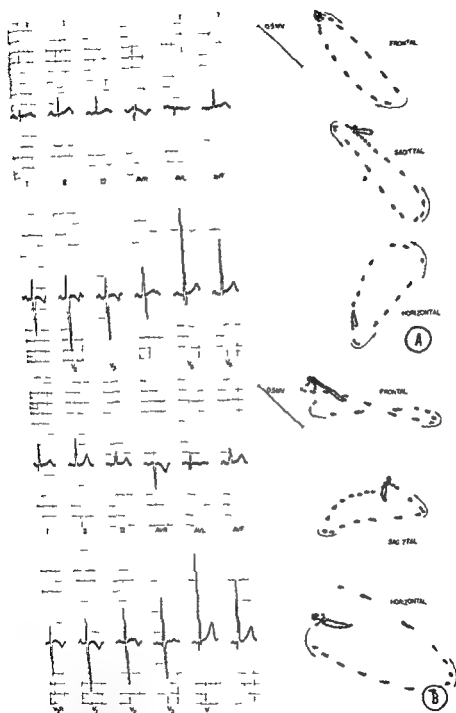


Fig 3 A and B ECG and VCG in two subjects with left ventricular hypertrophy determined by magnitude of precordial voltage. A Subject J W ECG demonstrates tall voltages in left chest leads ($R_{V_4} = 24 \text{ mm}$) VCG shows a relatively narrow loop II rected posteriorly with a maximal spatial vector to the left of 170° mv. B Subject C M ECG shows tall voltages in left chest leads ($R_{V_4} = 30 \text{ mm}$) VCG = normal ECGs are recorded at standard $\times 2$.

We wish to thank Dr James J. Hudon Jr. of the Johns Hopkins Comprehensive Child Care Clinic Dr Shirley I. Backlund of the Johns Hopkins University Health Center and St. Vincent's Orphanage of Baltimore County for their cooperation and assistance in providing subject for this study. The valuable advice and direction provided by Dr Richard D. Kowars is greatly appreciated.

REFERENCES

- Ziegler R F. Electrocardiographic studies in normal infants and children. *Springfield Ill* 1951 Charles C Thomas
- Naiman F P and Miller K A. The normal electrocardiogram and vectorcardiogram in children. In Crisels D F and Ziegler R F, editors. *Electrocardiography in infants and children*. New York 1966 Grune & Stratton
- Burch G F and DePisquale A J. Electrocardiography in the diagnosis of congenital heart disease. *Philadelphia* 1967 Lea Febiger
- Alumung M M, Lester G J, Nicks A S and Wassell B F. The unipolar precordial and extremity electrocardiogram in normal infants and children. *Circulation* 11:420 1951
- Thomas J, Harrison F and Lassner G. Observations on the T wave and S-T segment changes in the precordial electrocardiogram of 320 young Negro adults. *Am J Cardiol* 5:468 1960
- Gottschalk C W and Cruikshank I. A comparison of the precordial S-T and T waves in the electrocardiogram of 600 healthy young Negro and white adults. *South Med J* 49:453 1956
- Lipberger H V, Goldman M J, Littman D, Murphy G P, Cosmi J and Snyder J R. Correlation of the orthogonal electrocardiogram and vectorcardiogram with constitutional variables in 518 normal men. *Circulation* 35:536 1967
- Wasserbarger R H. Observation on the juvenile pattern of adult Negro males. *Am J Med* 18:428 1955
- Doner G E, Moore A D, Ziegler W G and Osborne J A. On QRS amplitude and other errors produced by direct writing electrocardiographs. *Am Heart J* 65:307 1963
- Scher A M and Young A C. Frequency analysis of the electrocardiogram. *Circ Res* 8:344 1960
- Committee on Electrocardiography. American Heart Association. Recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography. *Circulation* 35:583 1967
- Altman P L and Dittmer D S, editors. *Respiration and Circulation*. Bethesda Md 1971. Federation of American Societies for Experimental Biology (Biological Handbooks) p 147
- Greene C R and Kelly J J. Electrocardiogram of the healthy adult Negro. *Circ* 20:906 1959
- Brink A J. The normal electrocardiogram in the adult South African Bantu. *S Afr J Clin Med* 2:9, 1956
- Sutin C J and Schrire V. The electrocardiogram in the first two days of life. An international study. *Am Heart J* 6:149 1961
- Walker A K P and Walker H F. The timing of race, sex, age and nutritional state in the electrocardiograms of young South African Bantu and Caucasian subjects. *Am Heart J* 77:441 1969
- Dharmadasa K and Nadarajah M. Electrocardiograms in young Ceylonese. *Br Heart J* 30:165 1968
- Pyke D A. Electrocardiographic changes in West Indian. *Proc R Soc Med* 56:67 1963
- Lipstein I H, Lofback A V and Osterweil D. An electrocardiographic study in Per. *Am J Med Sci* 217:681 1964
- Simonon E. Differentiation between normal and abnormal in electrocardiography. *Am Heart J* 1961 The C V Mosby Co pp 10 11 126 128
- Senkumta S G, Indumathi M and Gopal C. The electrocardiogram in some Indian population group. *Circulation* 29:118 1961
- Ashcroft M T, Miller G J, Bickel H M S G and Swann A V. A comparison of T wave inversion, ST elevation and K waves in precordial leads of Africans and Indians in Guyana. *Am Heart J* 81:167 1971
- Borun I P, Chipman J M and Vassal J J. Electrocardiographic data recorded with Frank leads in subjects without cardiac disease and in subjects with left ventricular overload. *Am J Cardiol* 18:656 1966
- Kelly S E and Lapechkin F. Effect of body build on the QRS voltage of the electrocardiogram in normal men. *Circulation* 31:11 1965
- Walker C H M and Rose R I. Importance of race, sex and body habitus in the diagnosis of left ventricular hypertrophy from the precordial electrocardiogram in childhood and adolescence. *Pediatrics* 28:105 1961
- Lynn M A, Murthy V, Clark J, Conforti G, Chae C and Bentley A F T. Body composition of Negro and White children. *Arch Intern Med* 20:604 1970
- Ichimura I, J. Barber M, K. Lehner H H. Effect of torso resistivity variation on the ECG of children using a grid lead system. *Circulation* (In press)
- Singhvi I M, Sharma I and Mitra S V. Cardiovascular disturbances in chronic essential hypertension. *Circulation* 15:373 1957
- Crisels D E and Ziegler R F, editors. *Electrocardiography in infants and children*. New York 1966 Grune & Stratton p 355
- Hugenholz I G and Gimbaras I. Effect of chronically increased ventricular pressure on electrical forces of the heart. *Circulation* 30:511 1964

Factors influencing hemolysis in valve prosthesis

Carlos Crexells MD
Arconius Ierichide MD
Yvette Bonny MD
Gilles Lepage MD
Lucien Campeau MD
Montreal Canada

In 1954 Rose and associates¹ reported for the first time hemolytic anemia associated with intracardiac valve prosthesis. This complication was then experimentally confirmed in dogs by Stohman and co-workers² in 1956. It is now a well recognized syndrome, but the etiological factors are still not well defined. The purpose of this study was to evaluate the hemolytic effects of prosthetic materials and designs.

Materials and methods

The 208 patients included in this study represent all the patients with valve replacement who attended the anticoagulant clinic from July 9, 1970 to Sept 13, 1970, a period arbitrarily chosen. They were from a group of 757 patients who had valve replacement in this hospital from Jan 4, 1962 to July 15, 1970.

The types and positions of valve prostheses are shown in Table I. The degree of hemolysis was evaluated in all these patients with various types of prostheses. But only the Starr Edwards and Beall prostheses were studied with respect to biological factors of hemolysis. The Beall

prosthesis is a Teflon disc valve with Teflon covered cage. Starr Edwards valves are of different types: (1) silicone elastomer ball uncovered cage models 1000, 1200 and 1260 for the aortic valve and models 6000, 6100 and 6120 for the mitral orifice; (2) Stellite ball Teflon covered cage models 6300 and 2300 for mitral and for aortic orifices respectively. These were reported as functionally stenotic^{3,4} and have been replaced recently by models 6310 and 2310. These newer models have a large orifice and a slight modification of the Teflon ring (composite seat).

Screening laboratory tests for evidence of hemolysis performed in all these patients comprised the following: (1) hemoglobin (Hb) and hematocrit (Hct); (2) free plasma hemoglobin by colorimetry (normal values less than 5 mg per 100 ml); (3) direct and indirect Coombs test; (4) serum lactate dehydrogenase activity (LDH) using the Cabaud Wroblewski method (normal values less than 500 u C W) and (5) serum hydroxybutyryl dehydrogenase (HBD) using Rosalki's technique⁵ (normal values less than 300 u).

Sixty-eight patients had normal results

Received for publication July 1, 1971. Accepted for publication Oct 4, 1971.

Reprint requests to Dr. Carlos Crexells, MD, St. Paul St. Eustache, Montreal, Canada.

Table I *Types and positions of single and multiple prostheses*

Positions	Starr Edwards			Ball	Surgitool	Hufnagel	Magovern	Others
	Silicone elastomer ball	Stellite ball	Disk					
Isolated								
Mitral (M)	51	36	2	12	—	1	—	—
Aortic (A)	33	27	—	—	1	2	1	—
Tricuspid (I)	2	—	—	—	—	—	—	—
							Total = 171	
Multiple								
M + A	13	6	—	—	—	—	—	1
M + I	—	—	—	3	—	—	—	1
M + A + I	—	—	—	—	—	—	—	5
							Total = 17	

Table II *Criteria of hemolysis*

Variables	Mild hemolysis	Severe hemolysis
SI DH activity (I/II < 0.8)	500–1500 u	> 1500 u
Free plasma Hb	< 50 mg/100 ml	> 50 mg/100 ml
Urinary Hb	absent	present
Reticulocytes	1–5–10%	> 10%
Plasma total bilirubin	1–3 mg/100 cc	> mg/100 cc
Schistocytes	absent	present

and no other tests were performed. In 140 patients in whom one or more of the above parameters were abnormal, the same tests were repeated and the following investigation was also carried out:

(1) Colorimetric ratio of SLDH subunits (Profile SLDH, General Diagnostics)^{7,8} Normal ratios of I over II subunits are 0.8 to 1.2. Ratios of less than 0.8 suggest II subunits predominance and are compatible with hemolysis, muscle injury, renal infarction, and megaloblastic anemia.

(2) Peripheral blood smear for search of schistocytes and megaloblastosis.

(3) Reticulocyte count (normal values less than 1.5 per cent).

(4) Total and direct bilirubin levels were determined by Hodge and Matthes method⁹ (normal values less than 0.8 and 0.2 mg per 100 ml, respectively).

(5) Qualitative determination of urinary hemoglobin.

(6) Serum haptoglobin was also determined in 19 cases by immunodiffusion

(Partigen, Behringwerke AG)¹⁰ (normal values between 20 and 204 mcg per 100 ml).

The criteria of hemolysis and of its severity were determined as indicated in Table II. It was evaluated primarily by the SI DH levels whenever I/II was smaller than 0.8. SLDH activity¹¹ correlates well with erythrocyte survival time. SI DH levels of 500 u and less represent normal half life levels of 500 u to 1500 u correspond to 15 to 25 days, considered as mild hemolysis and levels greater than 1500 u correspond to a survival of less than 15 days reflecting severe hemolysis.¹² In a few cases of normal SI DH activity or discordant liver/heart (I/II) ratio, the diagnosis of hemolysis was based on the other parameters.

Anemia was defined by a Hb of less than 10.5 Gm per cent. Therapy of anemia was not considered because of the various iron preparations and dosages.

All patients were ambulatory. All had a

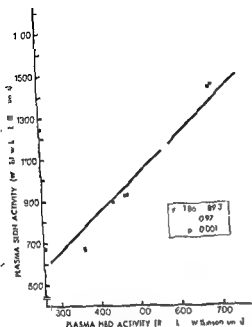


Fig 1 The relation between SLDH activity (L/H subunit ratio < 0.8) and HBD in 63 consecutive cases

phonocardiogram using an Electronics for Medicine five channel photographic recorder to detect signs of ball variance²². Acute myocardial infarction was excluded by history and ECG.

Results

1 Incidence and degree of hemolysis Of the 208 patients studied 140 (67.3 per cent) showed unequivocal signs of intravascular hemolysis. Severe hemolysis was present in 22.4 per cent. All these 140 cases except 4 had abnormally high SLDH levels. The SLDH subunits ratio determined in these 136 patients was abnormal with H predominance (L/H < 0.8) in 114, abnormal with L predominance (L/H > 1.2) in 4, whereas it was normal in 18. An excellent correlation existed between SLDH and HBD plasma levels (Fig 1). SLDH levels with L/H ratio < 0.8 plotted against free plasma hemoglobin were found also highly significant (Fig 2). However only 3 patients had circulating hemoglobin exceeding 50 mg per 100 ml. Urinary Hb determined qualitatively in 140 patients was positive in only 26. Almost all these 26 patients presented high levels of SLDH and free Hb

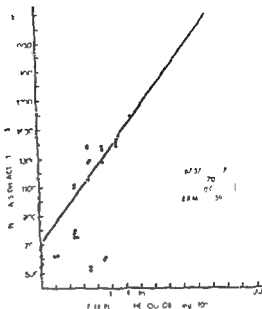


Fig 2 The relation between SLDH activity and free plasma hemoglobin in 119 consecutive cases

was present often in high amounts but no correlation was found between urinary Hb and the other parameters. Since only 19 patients had plasma haptoglobin determinations (mean 9.73 mcg per 100 cc) the correlation between haptoglobin and urinary hemoglobin was not attempted. Bilirubin determination was made in 140 patients. In only 26 did the total bilirubin exceed 0.8 mg and although SLDH, HBD and plasma hemoglobin levels were high in all cases, no correlation was found between these parameters. The highest total and direct bilirubin values were 2.25 mg and 1.20 mg per cent respectively.

Forty-one and four tenths per cent of these 140 patients with hemolysis had an abnormal Hb (< 13 Gm per cent). 17 patients had a Hb between 10.5 and 12 Gm per 100 ml, and 31 had Hb levels between 12 and 13 Gm per 100 ml. In only 7.1 per cent was it significantly low (< 10.5 Gm per 100 ml).

Reticulocyte count in the peripheral blood smear was superior to 1.5 per cent in 133 of 136 cases. The highest value was 11.8 per cent and the mean value for the group was 3.84 ± 0.23 SEM. No correlation was found between reticulocyte count and SLDH levels. Schistocytes were

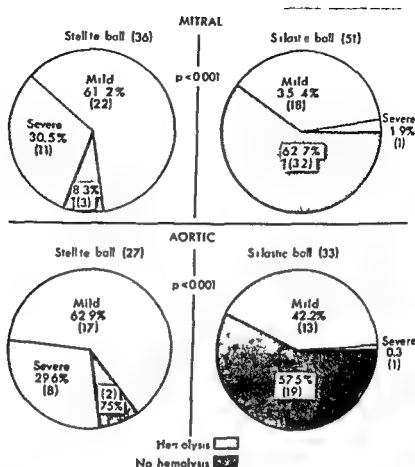


Fig 3 Comparison between the degree of hemolysis produced by silicone elastomer ball uncovered and Stellite ball covered Starr Edwards valve. Statistical analysis was performed by chi square test.

present in only 17 of 140 patients who had their peripheral blood smear examined. Of these 140 patients, 10 had a Hb level of less than 10.5 Gm per 100 ml and of these 9 had schistocytes. All had more than 2,000 μ SLDH and a high percentage of reticulocytes. Megaloblastosis was excluded in all these cases. Direct Coombs test was negative in all of 203 patients, although 10 had a positive indirect test.

In summary, the diagnosis of hemolysis was based on an increased SLDH activity with L/H < 0.8 in 114 patients. In the other 26 patients, hemolysis was determined by increased HBD levels, free plasma hemoglobin and high reticulocyte count.

2 Influence of the types of prostheses and its materials. All 12 patients with a mitral Beall prosthesis had hemolysis: mild in 6 and severe in the other 6. Mean SLDH level was 1594 ± 123 (S.L.M.) which is higher than the mean SLDH level found in cases of multiple prostheses, irrespective of their types. One of the patients with a

Beall valve had severe hemolytic anemia resistant to iron therapy.

The incidence and degree of hemolysis were greater in cases of Stellite ball covered valves as compared to those of silicone elastomer ball uncovered prostheses, irrespective of position, aortic or mitral (Fig 3). SLDH activity was significantly higher in cases of Stellite Teflon covered prostheses for aortic valves as well as for mitral valves (Fig 4).

3 Influence of the position of the prostheses. No significant difference was found between 67 aortic and 101 mitral prostheses of all types (Fig 5). The same results were observed when comparing mitral to aortic Starr Edwards valves as a group and when these valves were studied separately as Stellite ball covered valves and as silicone elastomer ball uncovered valves.

4 Influence of number of prostheses. Of 37 patients with a double prosthesis (including all models of valves), 26 (51.2 per cent) presented hemolysis of which half was severe. Hemolysis was found in 109 of 141

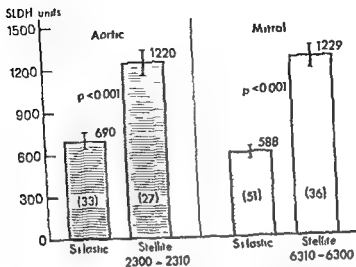


Fig. 4 Comparison between SLDH level found in patients with Starr Edwards mitral and aortic valves. Significantly higher levels of SLDH were found for Stellite valve Teflon covered prostheses (t test)

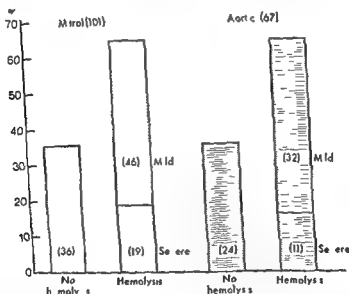


Fig. 5 Degree of hemolysis found in patients with mitral and aortic prostheses irrespective of design

es of single prosthesis (63.7 per cent). DH activity was significantly higher in it group as compared to the single valve group (Fig. 6). Four patients had severe hemolytic anemia in this group of double prosthesis (12.5 per cent) contrasting with an incidence of 3.3 per cent in the single valve group.

Double mitral and aortic Starr Edwards bicone elastomer ball valves hemolyzed

more than single mitral and aortic valves of the same model (Fig. 7) but no difference was noted between Stellite ball covered valves (1615 ± 154 versus 1224 ± 60 S.E.M. SLDH u).

The incidence of hemolysis was similar for triple and double valve prostheses including all models.

5. Influence of valve orifice size: The only significant difference with respect to orifice

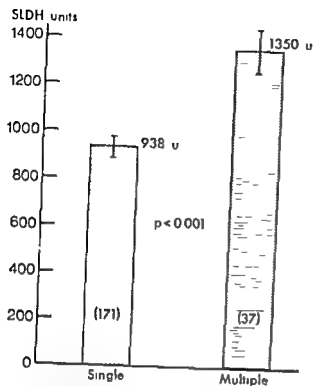


Fig 6 SLDH activity found in patients having a single and a multiple valve replacement irrespective of the type (t test)

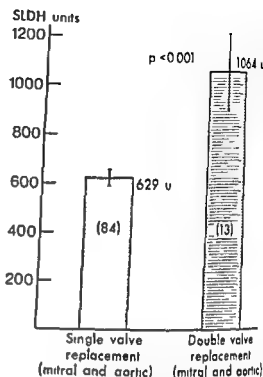


Fig 7 SLDH activity found in patients having single and double (mitro-aortic) Starr Edwards Stellite ball uncovered prostheses (t test)

size was observed between the 2300 and the 2310 models of the aortic Starr Edwards Stellite ball valves. The 2300 model having a smaller orifice had a significantly higher incidence of hemolysis (Fig 8). This was not observed for mitral valve models 6300 and 6310 having similar orifice size differences.

6 Other factors studied The mean time elapsed since the operation was not different between the hemolyzing and non hemolyzing prostheses. Bill variance was not observed by phonocardiographic screening. Prosthesis dysfunction was not suspected clinically and it was not found in the 12 patients who had a postoperative hemodynamic study. The influence of rhythm was not studied.

Discussion

Subclinical hemolysis was detected in 67 per cent of these 208 patients. This finding is in agreement with previously reported series.¹⁴⁻¹⁹ Chronic hemolytic anemia resistant to iron therapy was present in only 5 per cent of our patients, an incidence similar to that reported by Rodgers and Sabiston.²⁰ The best method for estimating the degree of hemolysis is the erythrocyte survival time obtained by ⁵¹Cr.²¹ Shortened

erythrocyte half life has been reported also in severe unoperated rheumatic heart diseases.^{18, 22} However, this method although very sensitive, is expensive and time consuming. It appears that total SLDH activity gives a reliable approximation of erythrocyte survival time.^{11, 12} It is unfortunately much less specific since it is also increased by disorders involving liver, kidney, skeletal and cardiac muscle.² The specificity of the test may be fostered by determining its origin by electrophoretic separation of its isoenzymes²³ or by fractionation of II and I subunits (by heat or substrate inhibitors).^{24, 25} The latter method was used in this study. In addition faster moving LDH isoenzymes reduce alpha-ketobutyrate more readily than slow moving ones and thus the quantitation of this reaction may be expressed as alpha hydroxybutyrate dehydrogenase activity (HBD).²⁶ Consequently, plasma LDH originating from heart, kidney and erythrocyte should correlate well with HBD levels, a fact confirmed in this study as shown in Fig 1.

Free plasma hemoglobin liberated from erythrocytes binds to haptoglobin or is excreted by the kidney whenever the plasma levels exceed the binding capacity.

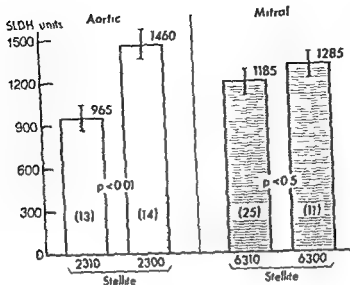


Fig 8 Difference between two models of Stellite ball covered prostheses were apparent only for the aortic group (t test)

of this protein. Normally, sufficient haptoglobin is present to bind 100 to 150 mg of hemoglobin per 100 cc.²⁸ As shown in Fig 2 we found a relatively good correlation between SLDH and free Hb although the degree of dispersion suggests that haptoglobin production or its ability to bind free Hb may be different from patient to patient with chronic hemolysis. Haptoglobin levels were determined in only 19 cases and were found decreased in cases with high SLDH activity. Slight hyperbilirubinemia was observed in a few cases as expected since only slight to moderate hemolysis of extravascular origin is observed in these cases of valve prostheses.^{26,27}

Abnormal erythrocyte morphology may be observed in peripheral blood smear in cases of hemolysis.²⁸ As in microangiopathic anemia fragmented red cells or schistocytes always reflect intravascular hemolysis but usually when it is severe.⁹ In our experience SLDH activity has been more reliable. In this series only 12 per cent of the patients presenting with hemolysis had schistocytes. All of these showed severe erythrocyte destruction and 50 per cent had significant hemolytic anemia (Hb < 10.5 Gm per 100 ml). This latter finding, in contrast with the 71 per cent incidence of severe anemia in patients with hemolysis. Although microangiopathic anemia and intravascular hemolysis following pros-

thetic valve replacement have some features in common they differ in that the erythrocyte fragmentation in the former condition is associated with fibrin deposits and hypofibrinogenemia as described by Brain.²⁹ In contrast patients with prosthesis hemolysis show a tendency to hyperfibrinogenemia secondary to a low rate catabolism or to an increased synthesis.³¹

Increased turbulence generated by the impact of red cells on rough and hard surfaces has been incriminated as the most important etiologic factor of this hemolytic phenomenon associated with valve prosthesis.^{13,20,32} Greater hemolysis during exercise has been reported particularly in cases of aortic prostheses.^{13,17,33} In the presence of ball variance and in paravalvular leaks.^{22,33} These facts favor the turbulence hypothesis which indirectly is also supported by the observation that properly functioning heterografts are only slightly hemolytic.³⁰ Hemolysis has also been experimentally produced by Bull³⁴ using a pump system where turbulence is created by a rapidly moving blood stream in the presence of an obstruction. The autoimmune mechanism involving erythrocyte antibodies generated by antigenically active red cell fragments suggested by Pyrofsky and associates^{42,43} in 1962 may be a secondary phenomenon.

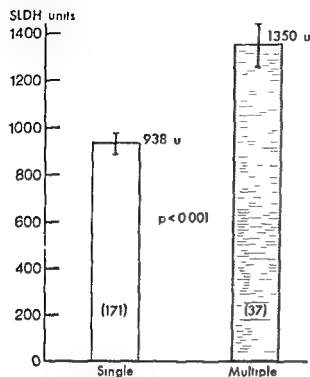


Fig 6 SLDH activity found in patients having a single and a multiple valve replacement irrespective of design (t test)

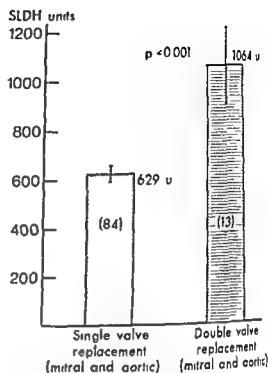


Fig 7 SLDH activity found in patients having single and double (mitro-aortic) Starr Edwards Stellite bill uncovered prostheses (t test)

size was observed between the 2300 and the 2310 models of the aortic Starr Edwards Stellite bill valves. The 2300 model having a smaller orifice, had a significantly higher incidence of hemolysis (Fig 8). This was not observed for mitral valve models 6300 and 6310 having similar orifice size differences.

6 Other factors studied The mean time elapsed since the operation was not different between the hemolyzing and non hemolyzing prostheses. Bill variance was not observed by phonocardiographic screening. Prosthesis dysfunction was not suspected clinically and it was not found in the 12 patients who had a postoperative hemodynamic study. The influence of rhythm was not studied.

Discussion

Sublethal hemolysis was detected in 67 per cent of these 208 patients. This finding is in agreement with previously reported series.¹¹⁻¹³ Chronic hemolytic anemia resistant to iron therapy was present in only 5 per cent of our patients, an incidence similar to that reported by Rodgers and Sabiston.¹⁰ The best method for estimating the degree of hemolysis is the erythrocyte survival time obtained by ⁵¹Cr.¹⁴ Shortened

erythrocyte half life has been reported also in severe unoperated rheumatic heart diseases.^{15,16} However, this method although very sensitive is expensive and time consuming. It appears that total SLDH activity gives a reliable approximation of erythrocyte survival time.^{11,12} It is unfortunately much less specific since it is also increased by diseases involving liver, kidney, skeletal and cardiac muscle.¹⁷ The specificity of the test may be fostered by determining its origin by electrophoretic separation of its isoenzymes,¹⁸ or by fractionation of H and L subunits (by heat and substrate inhibitors).^{19,20} The latter method was used in this study. In addition fast moving LDH isoenzymes reduce alpha-ketobutyrate more readily than slow moving ones and thus the quantitation of this reaction may be expressed as alpha hydroxybutyrate dehydrogenase activity (HBD). Consequently plasma LDH originating from heart, kidney and erythrocyte should correlate well with HBD levels. A fact confirmed in this study, as shown in Fig 1.

Free plasma hemoglobin liberated from erythrocytes binds to haptoglobin or is excreted by the kidney whenever the plasma levels exceed the binding capacity

Summary

Hemolysis was found in 67.3 per cent of 208 patients with valve prosthesis. The diagnosis of hemolysis was based on an increased serum lactic dehydrogenase activity (LDH) with sub unit liver/heart < 0.8 in 114 patients. In the others it was determined by increased serum hydroxybutyryl dehydrogenase (HBD), free plasma hemoglobin and abnormally high reticuloocyte count. Excellent correlations existed between LDH and HBD plasma levels on the one hand and between LDH levels and free plasma hemoglobin on the other. Significant hemolytic anemia (hemoglobin < 10.5 Gm per 100 ml) was observed in only 5 per cent of these patients irrespective of iron replacement therapy. The Beall mitral prosthesis was found the most prone to hemolysis, a complication observed in all 12 cases studied. The Starr-Edwards Stellite ball Teflon-covered valve hemolyzes significantly more than the silicone elastomer ball uncovered prosthesis in the aortic and mitral positions. It is felt that the Teflon covering may be an important hemolytic factor in both Starr-Edwards model and Beall prostheses.

The authors wish to thank Dr Paul David, General Director, Montreal Heart Institute and Dr Pierre Simard, Chief of Clinical Laboratories, Montreal Heart Institute as well as Dr Joseph Pellerin for their support and collaboration in this study. We are also grateful to Mr Samir Naoum, Mr Raymond Guay and Mr Luc Dumais for their technical help and assistance.

REFERENCES

- Rose J C, Hufnagel C A, Fries E D, Marvey W P and Partonope E A. The hemodynamic alterations produced by a plastic valvular prosthesis for severe aortic insufficiency in man. *J Clin Invest* 33:391 1954.
- Stohliman F, Satnoff S J, Case R M and Ness A T. Hemolytic syndrome following the insertion of a lucite ball valve prosthesis into the rat aortic system. *Circulation* 13:586 1956.
- Kloster F F, Herr R M, Starr A and Griswold H E. Hemodynamic evaluation of a cloth covered Starr-Edwards valve prosthesis. *Circulation* 39:119 1969.
- Reis R, Clancy D L, O'Brien K, Epstein S E and Morrow A G. Clinical and hemodynamic assessments of fabric covered Starr-Edwards prosthetic valves. *J Thorac Cardiovasc Surg* 64:84 1970.
- Cabaud P G and Wroblewski F. Colorimetric measurement of lactic dehydrogenase activity of blood fluid. *Am J Clin Pathol* 30:334 1958.
- Josalki S B. A simple colorimetric method for the determination of serum alpha hydroxybutyric dehydrogenase. *J Clin Pathol* 15:666 1962.
- Bibson A I and Phillips G F. A rapid colorimetric assay for serum lactic dehydrogenase. *Clin Chim Acta* 12:110 1965.
- Bibson A I and Phillips G F. The chemical differentiation of tissue lactic dehydrogenase. *Clin Chim Acta* 16(1):121 1966.
- Hogge C K and Meites S. Modification of the "Mal" and "Felym" procedure for the micro determination of total serum bilirubin. *Am J Med Technol* 28:781 1959.
- Schwick G and Storiko K. Qualitative and quantitative determination of plasma proteins by immunoprecipitation. *Lab Synops* 1:1965.
- Mjyre E and Rasmussen K. Serum lactic dehydrogenase activity and intravascular hemoglobin in *Lancet* ii:355 1970.
- Mjyre E, Rasmussen K and Andersen A. Serum lactic dehydrogenase activity in patients with prosthetic heart valves. A parameter of intravascular hemoglobin. *Am Heart J* 80:463 1970.
- Najmi M and Segal B I. Auscultatory findings in patients with prosthetic ball valves. *Am J Cardiol* 16:1794 1965.
- Yacoub M H and Keeling D H. Chronic haemolysis following insertion of ball valve prostheses. *Br Heart J* 30:676 1968.
- Mjyre E and Rasmussen K. Mechanical hemoglobin in aortic valvular disease and aortic ball valve prostheses. *Acta Med Scand* 186:543 1969.
- Cullhed I. Serum haptoglobin in cases with Starr-Edwards ball valve prosthesis. *Acta Med Scand* 181:371 1967.
- Bell R E, Petrucci S and Fraser R S. Chronic haemolysis occurring in patients following cardiac surgery. *Br Heart J* 29:377 1967.
- Brodeur M T H, Sutherland D W, Koler R D, Starr A, Himsey J A and Griswold H E. Red blood cell survival in patients with aortic valvular disease and ball valve prosthesis. *Circulation* 32:570 1965.
- Andersen M N, Gabrieli E and Zizzi J A. Chronic hemolysis in patients with ball valve prosthesis. *J Thorac Cardiovasc Surg* 50:501 1965.
- Rodgers B M and Sabiston D C. Hemolytic anemia following prosthetic valve replacement. *Circulation* 39 (Suppl 1):155 1969.
- Mollison P L. Measurement of survival and destruction of red cells in hemolytic syndrome. *Br Med Bull* 15:59 1959.
- Dameshek W. Case record of Massachusetts General Hospital. *N Engl J Med* 271:898 1964.
- Wroblewski F. The clinical significance of alteration of LDH activity of body fluids. *Am J Med Sci* 231:301 1957.

Our findings suggest that prosthetic materials may be major determinants of this hemolytic syndrome. Hemolysis is significantly more prevalent in cases of Stellite ball Teflon covered Starr Edwards valves compared to the silicone elastomer ball cage prosthesis irrespective of their mitral or aortic position. These prostheses being different in two respects the ball material and the Teflon covering, the relative importance of these characteristics with respect to hemolysis is difficult to assess. It is possible, as suggested by Myhre and co-workers⁴⁴ that the impact on red blood cells by the metallic ball is greater and is thus more hemolyzing. The aortic and mitral position of the prosthesis may not differ in this respect. On the other hand, Teflon covering may also produce hemolysis by lack of epithelium covering as previously reported for Teflon patches closing in atrial and interventricular septal defects.⁴⁵ Be this as it may the Stellite ball and Teflon covered prostheses are definitely more prone to hemolysis and it appears that the Teflon covering may be the most important factor. It also seems that these characteristics are more significant than the hemolytic effect of increased turbulence at least in these prostheses. In fact the aortic valve produces more turbulence as compared to the mitral⁴⁶ and yet identical mean SLDH levels were found for Starr Edwards metallic ball cloth covered aortic and mitral prostheses. Likewise no statistically significant difference was found between the mitral and the aortic silicone elastomer ball uncovered valves although SLDH levels in the aortic prosthesis were slightly superior. This slight difference for uncovered prostheses which are less prone to hemolyze may be explained by the increased turbulence at the aortic position. Hemolysis most likely associated with turbulence was noted in cases of aortic Starr Edwards model 2300 which has a covered cage but is in addition functionally stenotic.^{3,4} Double prostheses aortic and mitral, as compared to single aortic and mitral prostheses show a higher degree of hemolysis only for the cases of stellite ball uncovered prostheses which as previously mentioned, are less prone to hemolysis. The turbulence factor is most likely more prevalent in these double prostheses

and explains the higher degree of hemolysis. However, no significant difference was noted in cases of metallic ball Teflon covered valves, suggesting that the Teflon covering and the Stellite ball characteristics prevail over the turbulence factor. The hemolytic effect of turbulence may not be decreased in the presence of Teflon covering since hemolysis is more frequently observed in such cases, but it appears to be overshadowed by the effects of the Teflon and/or of the Stellite ball and thus it may not be recognized. The Beall prosthesis a disc valve but which also has a Teflon covered cage is likewise very hemolyzing.¹¹ SLDH levels found in this group were higher than those observed in plurivalvulars when turbulence may play an important role. Mitral gradients have been documented after Beall valve replacement⁴⁰ and hemolysis may certainly be due at least in part to increased turbulence. But their hemolytic tendency is so great that turbulence does not appear to be the only factor, and possibly not the most significant. It therefore seems that Beall valves combine two hemolyzing factors, one related to turbulence and the other to the cage covering and this association may explain their greater tendency to hemolyze. It may be that the Teflon covering is the most important hemolytic factor in both Starr Edwards and Beall prostheses since this characteristic is common to both.

Hemolysis associated with valve prosthesis is well tolerated and responds well to iron replacement therapy. If severe the bone marrow cannot compensate by increased erythropoiesis and resistant anemia develops. Tachycardia secondary to anemia may increase turbulence and hence the hemolytic process. Other forms of treatment specifically steroids^{20,21} and splenectomy^{21,22} have not been successful.

Long term effects of chronic intravascular hemolysis have not yet been completely established. Anemia and renal hemosiderosis seem to be its major harmful effects. Anemia resistant to iron treatment is present only in a small percentage of cases and renal hemosiderosis does not seem to impair renal function.¹ However long term effects of hemosiderinuria have not yet been adequately documented.

The incidence of hypertension and associated factors

The Israel ischemic heart disease study

Harold I Kahn MA *

Jack H. Medahe MD MPH**

Henry A. Neufeld M D ***

Tgon Riss M D M Sc ****

Uri Goldbourt U A **

Jerusalem Israel

Scientific reports on the incidence of hypertension are extremely uncommon. In the present paper we have used available data from a large scale prospective study focussed principally on coronary heart disease to add to existing knowledge about hypertension incidence. We are fully conscious of the limitations implied in our dependence on single casual blood pressure readings to define persons at risk and persons developing elevated blood pressure levels but single casual readings have been shown to be valuable tools in the analysis of coronary heart disease incidence.¹ Perhaps they can be usefully employed in the definition and study of hypertension incidence as well.

Methods

The data are from a five year prospective study of 10 000 Israeli male civil service workers which has been described else-

where? Briefly the study design took advantage of the heterogeneity of backgrounds in the Israeli population and selected men born in six areas: Israel, Asia, except Israel, Africa, Eastern Europe, Central Europe, and Southern Europe, from a population of male civil service employees aged 40 and over in 1963. The population included such diverse groups as dockworkers, clerks, street cleaners, and judges, so the common picture of a civil service employee as a sedentary clerical worker is not completely applicable in this study.

Blood pressures were measured on the right arm (with the subject lying down) at examinations in 1963, 1965 and 1968 by the method recommended by WHO¹ reading the pressure at eye level. Systolic pressure was measured at the onset of the sounds and diastolic pressure at the point of disappearance of the Korotkoff sounds.

Ministry of Health, Israel, and the Ministry of Health, Israel, and the National Health

This study was supported by HL-490 C to part F d Rese h Ag m t N 375106

Rec'd f p b1 el Oct 6 1971

R p r t e q u i s t H a r M A K a h M A C h f O f f i c e f E m t r y a d E p i m l g y B l l g 31 R o o m 6 A 10
N t i o n a l E y I t i t e I n s t i t u t o f H a l t h B t h e n d a M i 70014

National Eye Institute Bethesda Md (Form add National Heart, Lung & Blood Institute)

⁶⁶Department of Family Medicine TIA Medical School d H d nah Med cal O gan

Heart 1 still in THE born Hospit 1, Tel Aviv 1 1

at t t t R m b m H ; h L H f I r a L

- 24 Iretton J A, Brice R O and Butzki J G Rapid electrophoretic separation of lactic dehydrogenase on cellulose acetate *Am J Clin Pathol* 43:256 1965
- 25 Latham W and Worley W I The distribution of extracorporeal hemoglobin in circulating plasma *J Clin Invest* 38:474-652 1959
- 26 Wallace H W, Coburn R F, Habboushe F, Blakemore W S and Shephard C L Mechanically induced intravascular and extravascular hemolysis in dogs *Circ Res* 26:347 1970
- 27 Wallace H W Quantitation of red blood cell destruction associated with valvular disease and prosthetic valve *Jr Thorac Cardiovasc Surg* 60:847 1970
- 28 Stevenson T D and Baker M J Hemolytic anemia following insertion of Starr Edwards valve prosthesis *Lancet* 2:982 1964
- 29 Moyette J L Etude de la fréquence des complications hémolytiques et de l'iso-immunisation dans les cardiopathies opérées *Nouv Rev Fr Hematol* 8:457 1968
- 30 Brain M C, Dicie J V and Hourihane D Microangiopathic hemolytic anemia The possible role of vascular lesion in pathogenesis *Br J Haematol* 8:358 1962
- 31 Tessier Y, Phornphimol I, Collet H, Marshall J and McDonald L Plasma fibrinogen after replacement of heart valves by grafts or prosthesis *Lancet* 5:17 1971
- 32 Eysters, E, Mayer K and McKenzie S Traumatic hemolysis with iron deficiency anemia in patients with aortic valve lesions *Ann Intern Med* 68:995 1968
- 33 Viner L D and Frost J Hemolytic anemia due to a defective teflon aortic valve prosthesis *Ann Intern Med* 63:295 1965
- 34 Reed W A and Dunn M Fatal hemolysis following ball valve replacement of the aortic valve, *J Thorac Cardiovasc Surg* 48:436 1964
- 35 Robinson R M, Morrow, A G and Gebel I Mechanical destruction of erythrocytes by incompetent aortic valve prosthesis *Am HEART J* 71:179 1966
- 36 Sears D A and Crosby W H Intravascular hemolysis due to intracardiac prosthetic devices *Am J Med* 39:341 1965
- 37 De Cesare W, Rath C and Hufnagel C Hemolytic anemia of mechanical origin with aortic valve prosthesis *N Engl J Med* 272:1045 1965
- 38 Garcia M C, Chryste A M and Alexander C S Hemolytic anemia due to progressive enlargement of silastic ball component of aortic prosthesis *Circulation* 38:505 1968
- 39 Eysters, L Traumatic hemolysis with hemoglobinuria due to ball variance *Blood* 33:591 1969
- 40 Roesser W H P, Lowell L W and O'Brien M F Hemolysis after heterograft and prosthetic valve replacement *Am HEART J* 9:781 1970
- 41 Bull, B S Microangiopathic hemolytic anemia Mechanism of red cell fragmentation in vitro studies *Br J Hematol* 11:643 1968
- 42 Pirofsky B Aortic valve surgery and autoimmune hemolytic anemia *Am HEART J* 70:426 1965
- 43 Pirofsky B, Sutherland D W, Starr A and Griswold H E Hemolytic anemia complicating aortic valve surgery *N Engl J Med* 272:235 1965
- 44 Myhre L, Dale J and Rismu sen K Erythrocyte destruction in different types of Starr Edwards aortic ball valves *Circulation* 42:450 1970
- 45 Sigler A T, Forman E N, Zinkham W H and Neill C A Severe intravascular hemolysis following surgical repair of endocardial cushion defects *Am J Med* 35:467 1963
- 46 Verdon T A, Forrester R H and Crosby W H Hemolytic anemia after open heart repair of ostium primum defects *N Engl J Med* 269:444 1963
- 47 Sydes H M, Dicie J V, Handley D A, Lewis S M and Cleland W P Hemolytic anemia of mechanical origin after open heart surgery *Thorax* 16:356 1961
- 48 Smoloff E A, Dwyer F B and Kaufman B in Brewer I A editor Prosthetic heart valves Springfield, Ill 1969 Charles C Thomas p 10
- 49 Williams J C Jr, Vernon C R, Darrow G R et al Hemolysis following mitral valve replacement with the Beall valve prosthesis *J Thorac Cardiovasc Surg* 61:393 1971
- 50 Linhart J W, Barold S S, Hildner F J, Samet I, Iaccarini J C, Marsten J L and Greenberg J J Clinical and hemodynamic findings following replacement of mitral valve with Beall valve prosthesis *Circulation* 39(1):127 1969
- 51 Dicie J V The hemolytic anemias 2nd ed Part III New York 1967 Grune & Stratton p 954
- 52 Roberts W C and Morrow A G Renal hemosiderosis in patients with prosthetic aortic valves *Circulation* 33:390 1966

nurses subjects were asked about the number of portions of specific food items that they usually ate on a weekly basis. Portion sizes were referenced to food models on display and the numbers of small, medium or large portions of each food were first converted to grams of each food and then to nutrients for each food by means of multipliers stored in the computer memory and corresponding to gram units of each food. The nutrients for each food were then summed into a weekly total for each subject. All variables and measurements in the list refer to the 1963 examination.

- 1 Year of immigration to Israel 1938 or before
1939-1948 1949 and later
- 2 Number of children (includes stillbirths and those who have died) $\leq 1, 2, 3, 4+$
- 3 Number of persons living together (includes only those eating with you in your home) $\leq 3, 4, 5+$
- 4 Number of rooms in your home (excludes kitchen, bathroom, balconies and small entrance hall) $\leq 2, 3, 4+$
- 5 Weight/height ratio (kilograms/centimeters) $\leq 0.39, 0.40-0.45, 0.46+$
- 6 Triceps skinfold (in millimeters) $\leq 9, 10, 14, 15+$
- 7 Subscapular skinfold (in millimeters) $\leq 14, 15, 21, 22+$
- 8 Total serum cholesterol (in milligrams per cent) $\leq 189, 190-219, 220+$
- 9 Cholesterol in α -lipoprotein (in milligrams per cent) $\leq 31, 32-39, 40+$
- 10 Cholesterol in β -lipoprotein (in milligrams per cent) $\leq 149, 150-189, 190+$
- 11 Per cent of total cholesterol in α -lipoprotein (in milligrams per cent) $\leq 15, 16-19, 20+$
- 12 Uric acid (in milligrams per cent) $\leq 4.4, 4.5-4.9, 5.0+$
- 13 Hemoglobin (in grams per cent) $\leq 14.4, 14.5, 15.4, 15.5+$
- 14 Hematocrit (in per cent) $\leq 44, 45-46, 47+$
- 15 Persons per room (crowding index derived from No. 3 and No. 4) $\leq 1.00, 1.01-1.99, 2.00+$
- 16 Total protein (in grams per week) $\leq 649, 650-799, 800+$
- 17 Albumin protein (in grams per week) $\leq 299, 300-399, 400+$
- 18 Total fat (in grams per week) $\leq 499, 500-699, 700+$
- 19 Saturated fat (in grams per week) $\leq 159, 160-219, 220+$
- 20 Oleic acid (in grams per week) $\leq 179, 180-239, 240+$
- 21 Linoleic acid (in grams per week) $\leq 99, 100-159, 160+$
- 22 Total carbohydrate (in grams per week) $\leq 2, 199, 2, 200-2, 799, 2, 800+$
- 23 Carbohydrate from starch (in grams per week) $\leq 1, 399, 1, 400-1, 999, 2, 000+$

- 24 Eggs (in calories per week) $\leq 799, 300-499, 500+$
- 25 Bread (in calories per week) $\leq 3, 999, 4, 000-6, 999, 7, 000+$
- 26 Fats (in calories per week) $\leq 299, 300-699, 700+$
- 27 Rice (in calories per week) $\leq 199, 200-599, 600+$
- 28 Cereal (in calories per week) $\leq 199, 200-399, 400+$
- 29 Total calories (per week) $\leq 15, 999, 16, 000-20, 999, 21, 000+$
- 30 Per cent of calories from saturated fat $\leq 9, 10-17, 13+$
- 31 Ratio of linoleic to saturated fat $\leq 0.39, 0.40-0.69, 0.70+$
- 32 Ratio of saturated to unsaturated fat $\leq 0.51, 0.52-0.74, 0.75+$
- 33 Ratio of linoleic to total fat $\leq 0.33, 0.34-0.35, 0.36+$
- 34 Ratio of oleic to total fat $\leq 0.15, 0.16-0.21, 0.22+$
- 35 Ratio of saturated to total fat $\leq 0.31, 0.32-0.37, 0.38+$
- 36 Dietary salt. We wanted to obtain data on this variable but were unsuccessful in our efforts at quantification. For example, subjects were able to indicate how many eggs they usually ate per week but were not able to quantify for us how much salt was consumed with them.
- 37 Marital status. Divorced, widowed or bachelor, married once, married more than once.
- 38 Occupation. Administrative, professional, technical, laborer.
- 39 Subject's education. Elementary or less, partial or full high school, higher education.
- 40 Wife's education. Elementary or less, partial or full high school, higher education.
- 41 Wife's occupation. Housewife, additional work at home, works outside the home.
- 42 Hours per week of wife's outside work $\leq 19, 20-39, 40+$
- 43 History of heart attack (verified by survey staff from hospital or other medical records) No, yes.
- 44 History of peptic ulcer (partially verified by survey staff) No, yes.
- 45 Angina pectoris. Negative, suspect, definite.
- 46 Intermittent claudication. No, yes.
- 47 Cigarette smoking (excluding ex-smokers) Never, 1-10, 11-20, 20+.
- 48 Pulse rate (per minute) $\leq 70, 71-90, 91+$
- 49 Peripheral arterial disease. Negative, suspect, definite.
- 50 Emotional state (the number of positive answers to the questions—Do you consider yourself a tense person? Do you generally suffer from anxiety? Do you generally suffer from sleep problems [insomnia]?) 0, 1, 2, 3.
- 51 Past financial trouble. None (low), not serious, serious, very serious (high).

or of their missing in cases in which they did not disappear. This blood pressure was then recorded and the physical examination carried out. At the end of the examination and before blood taking, the blood pressure was measured a second time, approximately 15 to 30 minutes after the first using the same method. The second measurement* considered to be closer to a normal pressure has been used in the present paper. Methods related to quality control have been reported previously.⁴

There are many possible ways of investigating blood pressure changes or incidence of hypertension and they revolve around the question of definitions of hypertension who are the persons at risk, the variability of blood pressure estimations, and so on. The WHO has defined hypertension as readings at or above 160 mm Hg systolic and 95 mm Hg diastolic. The major objection to this definition is that it does not take age into consideration. While this is reasonable for use among communities where blood pressure does not rise with age its value may be limited for those areas where it does. What clinician would designate a 70 year old man with a blood pressure of 162/97 as a hypertensive? On the other hand, one might adopt figures which in all circumstances and ages would be agreed as being hypertensive e.g. a reading higher than 180/100. However whereas the latter is more specific, it would exclude many cases which clinically would be included as hypertension. A compromise might be adopted by defining hypertension as the upper 10 or 15 per cent of each age group by their blood pressure level which would thus vary by age. However this would tend to artificially equate incidence rates for all age groups.

The above definitions all depend on a specified level of pressure which in itself is questionable. A further technique therefore might be to measure the change in blood pressure from the last reading to the first. Here again there are problems as the amount of change is partly a function of the initial reading. The latter also influences the question of who is at risk when using

specified levels to define disease because obviously those initially nearest to the level specified will have more chance of crossing the critical point and being labelled as hypertensive.

As no one method appears to be the ideal one, we report here on incidence using the WHO definition and hope that in the future we shall be in a position to use some of the other methods and compare the results.

In this paper our interest is focused on individual rather than group changes and we have accordingly designated as at risk for hypertension incidence all individuals with 1963 blood pressures less than 140 mm Hg systolic and less than 90 mm Hg diastolic. As incidence cases we count those individuals who are found on subsequent examination to have pressures of 160 or more systolic and 95 or more diastolic in keeping with levels recommended by WHO.² More exactly those at risk in 1963 were counted as incidence cases if found to have 160/95 or more in 1968 or 160/95 or more in 1965 with the 1968 reading above the 139/89 levels or unknown. Those with both 1963 and 1968 readings unknown were removed from the population at risk reported herein.

Of the 10 059 men examined in 1963 95.3 per cent were examined again in 1968. An additional 2.8 per cent had died in the five year interval. Only 1.9 per cent were lost.⁵

An itemization of the variables reported in this paper other than age, race of birth and blood pressure is given below. For continuous variables the association with incidence of hypertension was calculated for the lower middle and upper third of the variable. Since these cutting points were determined for the total population in the study they are only approximately equal thirds for those at risk for incidence of hypertension. The cutting points for continuous variables as well as the 2, 3, 4 or 5 groupings studied for other variables are specified. Detailed description of data collection for many of the variables listed can be found in previous reports^{1,2,3} but because of its complexity we insert at this point an outline of the dietary data collection procedures. During a twenty minute interview conducted by specially trained

*In the 1965 examination only one measurement was made at a point in the examination equivalent to the second measurement on the 1963 and 1968 examinations.

1 May 84
1 May 82

period 1963-1968

Area of birth†	No at risk	Incidence per thousand (age-adjusted)	
		Five year	Approximate annual
Israel	566	37	7
Eastern Europe	683	61	13
Central Europe	511	61	13
Southern Europe	606	46	15
Africa	953	51	10
	510	9	1
Total	3 819	51	10

In investigating the relationships of many variables to the risk of developing hypertension as defined we have calculated hypertensive incidence rates (adjusted* for age and area of birth by the direct method to the total study population) for each of the classes designated in the Methods section. Both for numeric variables (such as No 5—weight/height ratio where the approximate tertiles were coded 1 2 3) and for coded variables with a clear ordering or direction (such as No 20—past financial trouble where the codes for none not serious serious and very serious were designated 1 2 3 4 respectively) we calculated the slope of the incidence rates on the independent variable, the standard error of the slope and the resultant *t* value. For other non numeric variables where the ordering of

classes had no directional sense to it (such as No 63—trying to improve job where the classifications are certain to succeed not certain to succeed not trying because no chance to succeed and not trying satisfied with present job) we calculated χ^2 for a $2 \times N$ contingency table.

No effort has been made to distinguish or to separate cases of secondary hypertension. The incidence cases reported herein are a mixture of essential and secondary cases.

Results

The incidence of hypertension (160 systolic or over and 95 diastolic or over) is shown in Table I by age group and by area of birth. Although there is an opinion to the effect that new cases of essential hypertension are rare after age 50* we find otherwise. On the assumption that our incidence cases like other groups reported are about 90 per cent essential and only about 10 per cent secondary cases^{10,11} the present data suggest that incidence of essential disease increases with age within the age span of a working population. The age adjusted five year incidence rates for the area of birth groups vary from a low of 28 per 1 000 for those born in Africa to a high of 76 per 1 000 for those born in Southern Europe. The three area groups with the highest rates were the three groups of men born in Europe.

Table 1 Age and area adjusted incidence of hypertension per 1,000 at risk in the five year

Age in 1963	No at risk	Incidence per thousand (area adjusted)*	
		Five year	Approximate annual
40-49	2,493	39	8
50-59	1,133	64	13
60+	204	102	20
Total	3,830	51	10

*For age differences: the probability that the slope of these rates are simply on a chance basis is <0.001
 †For area differences: $P(\chi^2)$ due to chance is <0.01

- 51 Present financial trouble None not serious
 serious very serious
- 52 Past family conflict None not serious serious
 very serious
- 53 Present family conflict None not serious
 serious very serious
- 54 Conflict with wife (keep to self) Always show
 outwardly (low) usually show outwardly
 usually keep it to myself always keep it to
 myself (high)
- 55 Hurt by family (brood) Usually forget tend
 to forget tend to brood usually brood
- 56 Hurt by family (retaliate) Very often some
 times seldom never
- 57 Hurt by family (restrain retaliation) Very
 often sometimes seldom never
- 58 Does wife show her love Very often seldom
 not enough never doesn't love me
- 59 Family listens to you Always usually some
 times never
- 60 Affected by family not listening Never hap
 pens not affected little upset very upset
- 61 Last work problems None not serious
 serious many serious
- 62 Present work problems None not serious seri
 ous many serious
- 63 Trying to improve job Certain to succeed not
 certain to succeed not trying because no
 chance to succeed not trying satisfied with
 present job
- 64 Co-workers show they like you Very often
 sometimes not as much as I would like
 never do not like me
- 65 Superiors show appreciation Very often
 sometimes not as much as I would like
 never do not like me
- 66 Past problems with co-workers None not seri
 ous serious many serious
- 67 Present problems with co-workers None not
 serious serious many serious
- 68 Past problems with superiors None not seri
 ous serious many serious
- 69 Present problems with superiors None not
 serious serious many serious
- 70 Hurt by co-workers (brood) Usually for
 (low) tend to forget tend to brood usually
 brood (high)
- 71 Hurt by superiors (brood) Usually forget
 (low) tend to forget tend to brood usually
 brood (high)
- 72 Hurt by co-workers (retaliate) Very often
 sometimes seldom never
- 73 Hurt by superiors (retaliate) Very often
 sometimes seldom never
- 74 Hurt by co-workers (restrain retaliation) never
 seldom usually always
- 75 Hurt by superiors (restrain retaliation) Never
 (low) seldom usually always (high)
- 76 Consider self a closed person Often talk
 sometimes talk generally yes yes
- 77 Problems in attaining desired living standard
 None some many very many
- 78 Fight injustice Never seen or not personally
 affected cannot do anything yes
- 79 Blood glucose (in milligrams per cent) ≤ 100
 130 150 160+
- 80 On diet No ulcer diet weight loss fat red
 tion heart disease or high blood pressure
- 81 After meal activity Work mixture of work and
 rest rest only
- 82 Computer ECG infarct Negative possible
 myocardial infarction (MI) probable MI
- 83 Computer LCC ischemia No yes
- 84 Computer ICC arrhythmia No yes
- 85 Computer ECG conduction defect Negative
 right bundle branch block (RBBB) left
 bundle branch block (LBBB) other
- 86 Computer ECG LVH Negative possible
 probable
- 87 Computer ECG AST No yes
- 88 Computer ECG left axis deviation No yes
- 89 Computer ECG summary Negative non
 specific T wave (NST) for 1 chemical possible
 MI probable MI or I BBB
- 90 Diabetes No abnormal glucose tolerance
 test yes

Table 11 Five year age and area adjusted hypertension incidence rates for variables* significantly ($P < 0.01$) associated with hypertension incidence

Variables (in three classes)	Five year incidence rates per thousand			Slope of incidence rates divided by the estimate of standard error of the slope (t value)
	Low	Middle	High	
Number of persons living in the same household	63 (1 087)†	56 (1 033)	40 (1 691)	-2.78
Weight/height ratio	29 (1 274)	51 (1 574)	95 (1 070)	6.18
Triceps skinfold	45 (1 243)	51 (1 197)	77 (1 147)	2.85
Subscapular skinfold	33 (1 523)	55 (191)	71 (1 984)	4.91
Uric acid	39 (1 741)	71 (873)	69 (1 163)	3.66
Pulse rate‡	39 (1 457)	67 (7 187)	113 (174)	4.30

Ordered variables (in four classes)	Low	Middle	High	
Cigarette smoking	41 (1 174)	43 (556)	57 (706)	2.60
Hurt by upper or (brood)	54 (954)	43 (937)	72 (670)	7.60
Hurt by superior (restrain retaliation)	35 (410)	63 (814)	81 (667)	2.98

* See Method section for full description of classification of each variable.
† Number of persons in each class.
‡ Ratio of mean diastolic blood pressure in the middle third of the distribution to the ratio of the lowest third of the distribution.

to detect true associations we have no reason to believe that our failures to find significant associations are necessarily similar to what we would have observed if we had been able to study hypertension rather than casual blood pressure readings. As a consequence we have a greater sense of security with respect to our findings of a significant association than we do with respect to our failure to observe a significant association. Accordingly our comments and comparisons with other reports in the literature are restricted to those variables which we find significantly associated with hypertension incidence.

The area of birth differences in observed incidence rates are similar in a gross way to those observed for incidence of myocardial infarction¹⁴ in that none of the three European groups had lower rates than the Asian, African, or Israeli groups. However the area differences with respect to hypertension incidence are much greater than they are with respect to myocardial infarction (MI). The ratio of highest to lowest five year rates for MI is 1.35 (Central Europe 0.030/Asia [except Israel]

0.037) but 2.71 (Southern Europe 0.076/Africa 0.028) for hypertension. Undoubtedly some of the greater variability in area incidence rates for hypertension reflects the smaller number of cases observed in the population at risk. Making allowance for the fact that we had no prior hypothesis that Southern Europe would be highest and Africa lowest for hypertension incidence this ratio is not significantly different from unity at the $p < 0.01$ level. In view of the fact that the mean blood pressure values among areas did not differ significantly¹⁵ we reserve judgment as to whether area differences in hypertension incidence are really so disparate as our raw data suggest. The finding that those born in Europe have higher hypertension incidence rates than those born in Israel elsewhere in Asia or in Africa is probably a real finding even though we presently lack a sense of the true size of the differential. Taken together with the similar finding about MI it opens an area for study as to factors present in these two groups that may explain the difference in incidence. Multivariate analyses of our data now in progress

In Table II we presented the five year age and adjusted incidence rates for specific levels of the nine variables found to be significantly associated with incidence of hypertension. Among the ninety variables listed in the 'Methods' section only these nine were associated with incidence to the degree that it would be observed by chance alone less than one time in a hundred. The variables are: No. 3—number of persons living together; No. 5—weight/height ratio; No. 6—triceps skinfold; No. 7—subscapular skinfold; No. 12—uric acid; No. 47—pulse rate; No. 46—cigarette smoking; No. 71—hurt by superior (brood) and No. 75—hurt by superior (restrain retaliation). All of these variables are subject to logical ordering and we have therefore calculated a weighted least squares regression coefficient* relating the hypertension incidence rate to a simple scale 1 2 3 or 1 2 3 4 for the independent variable. All of the relationships in Table II are positive except for variable No. 3 where the highest incidence rate was associated with the smallest size group of persons living together.

Because we are investigating so many variables we are concerned about the problem created by multiple significance tests where it becomes almost a certainty that something will be significant. To minimize the difficulties we have reported above and will consider in the discussion section to follow only those variables significant at $p < 0.01$. The variables associated with hypertension incidence for which the significance level is between 0.01 and 0.05 may simply be reflecting chance associations and unless these have previously been reported in other studies we refrain from commenting on them. They are listed below for the record so that subsequent incidence studies may note whether their association with hypertension is replicated. To the extent that they are it would be

profitable and desirable to then return these variables for further analysis. The variables in the significance range $p = 0$ to $p < 0.05$ are: No 1—year of immigration (longest residents tend to have highest incidence rates), No 4—number of rooms (positive association), No 8—serum cholesterol No 19—saturated fat (negative association), No 30—per cent of total calor from saturated fat (negative association), No 38—subject's education No 51—present financial troubles (negative association), No 54—conflict with wife (keep to 5), No 63—trying to improve job No 71—hurt by co workers (brood), No 97—specific T wave. One other association worth to mention is that for No 31—hematocrit. Its relationship to blood pressure incidence is clearly 'U' shaped. It is, both low and high values of hematocrit are associated with increased risk but had no prior hypothesis* to this effect and therefore make no comment as to its significance.

Discussion

At the outset it is important to emphasize that "incidence of hypertension" used in the title and elsewhere in this paper with reference to our study actually means incidence of elevated blood pressure. We are inclined to believe that the association found with elevated blood pressure in this population would also be found with essential hypertension in this population if it had been operationally feasible to define "litter" in terms of blood pressure levels always or almost always above the 160 level. Because of the obviously greater impact of measurement error in a single reading and the consequent loss of power

% of each of the three or four value of the variable was studied we have calculated an average adequately tell incidence rate. If there were no relationship between this variable and hypertension, the confidence interval of these incidence rate could expect to be 0. The weight of 1 / x squares means coefficient of this very type calculated under ordinary statistical formulae but with weight given to those incidence rates based on larger numbers of subjects and less to those based on a smaller number.

[illegible]

Table III Age specific and age and area adjusted five year hypertension incidence rates per 1000 in relation to number of persons living together and number of children

Age	No of persons living together			Slope of incidence rates divided by the estimated standard error of the slope (t value)
	13	4	59	
40-49	48	45	50	-1.95
50-59	69	94	49	-1.07
60+	143	37	57	-1.73
Total	63	56	40	-2.78

	No of children			
	01	23	49	
40-49	51	40	28	-2.07
50-59	76	72	37	-0.96
60+	93	119	123	0.54
Total	60	56	33	-0.66

of this association include cross sectional data from Framingham²⁴ and a report that patients with gout tend to develop renal insufficiency and hypertension²⁵ although after histological studies of renal biopsy tissue in hypertensives with gout and hypertensive patients without gout the latter report concludes that there is no evidence to explain the propensity of gouty individuals to develop hypertension.

In reporting the association between pulse rate and systolic blood pressure found in cross-sectional data from this study¹⁹ it was not certain whether or not the association reflected a mechanical increase in pressure when the pump was operating at a higher rate. The present data suggest that something more fundamental may be involved. Recent reports on this association include one on the cross sectional relationship in human beings²⁶ one on the cross sectional relationship in rats²⁷ and a plea to regularly include pulse rate as a variable for analysis in future blood pressure studies.¹⁹

The positive association we find between cigarette smoking and hypertension incidence contributes another fact to an area clouded by contrary findings. Large pro-

spective studies of mortality risk have reported an excess number of deaths from hypertension and/or hypertensive heart disease among cigarette smokers^{28, 29} while it is not uncommon for cross sectional studies to find no relation between cigarette smoking and blood pressure.^{30, 31} Possible but by no means necessary conclusions to be drawn from these facts are that (1) case fatality associated with hypertension and its sequelae among smokers may be high enough to obscure this relationship in cross sectional studies and (2) cross sectional studies may be recording smoking habits which have changed after disease onset.

It is now about 40 years since the first systematic studies of the relationship between personality and/or sociocultural factors to hypertension were reported. Many of these studies were based on small numbers of clinical cases, case control studies and other retrospective investigations after the onset of hypertension. The difficulties and problems of these have been detailed in a review of the field.³² Most of the studies found some differences between hypertensives and nonhypertensives although two studies were unable to demon-

ness, may help to shed some light on this matter.

We found one report which could reasonably be compared with our data as to level of incidence. This was derived from periodic health examinations offered by companies in the United States of America to their male employees.¹⁴ With those at risk defined as under 130 systolic, annual rates per 1,000 of 160 systolic or over or 95 diastolic or over or 'stated diagnosis (of hypertension) in the medical record were 5.7, 10.9, and 16.8 for ages 30 to 39, 40 to 49, and 50 to 59. Our five year incidence rates divided by five for rough approximation to annual rates are 7.8 for ages 40 to 49 and 12.8 for 50 to 59. With our group at risk defined as under 140 (tendency to give us higher rates) and our incidence cases defined as 160+ and 95+ (tendency to give us lower rates) it is difficult to say any more about this comparison than that the figures are of the same order of magnitude. Apart from level of rates, we note that our data confirm the finding from periodic health examinations that incidence rates go up with age in this age range.

Other reports on incidence of hypertension^{15, 16} were not comparable with our data, principally because of failure to provide age specific information or because persons with pressures just barely below the definition of hypertensive level were included in the population at risk.

Our finding of an inverse relationship between incidence of hypertension and 'number of persons living together' is consistent with earlier reports for males indicating an inverse relationship between average blood pressure and number of children¹ and prevalence of hypertension and number of children.²² Curiously enough, our own data relating number of children to hypertension incidence revealed no over all significant association. Looking at the data on number of children for specific age groups, however, showed that there was a significant negative association ($p < 0.05$) for age 40 to 49, a negative association but not strong enough to be significant at age 50 to 59 and a weak positive association at age 60+. These data together with the age specific data for number of persons living together are summarized in Table III. The data are consistent with the hypothesis that the

association is in fact with the size of the household rather than with the number of children. Evidently the other studies showed an association with number of children because the ages of their subjects as reported were substantially younger than ours. At younger ages the correlation between number of children and number of persons presently in the household is presumably much stronger than at older ages. On this basis, we can speculate that there is something in the interactions among many persons living closely together* that is inimical to the development of high blood pressure among males of the age groups in our study. It is also of some interest to note that in our study of the incidence of myocardial infarction we have also found a negative association with the number of persons living together.

As in our study, relative body weight and skinfold measurements have often been reported as positively related to hypertension.^{14, 23, 24} The judgment that the artifact of thick arms is only partly responsible for the association of blood pressure and obesity²⁵ is strongly supported by our incidence data which relate to measures of obesity and body size in a population entirely free of hypertension at the time of measurement. Looking at Table II we observe that both the weight/height ratio and the subscapular skinfold measurement are strongly related to hypertension incidence. The association with triceps skinfold is also positive and significant at the $p < 0.01$ level but is not nearly as strong as that for the other two measures of body size. Perhaps part of the explanation for this difference may be in the greater difficulty and hence greater measurement error in the determinations of the triceps skinfold in comparison to weight/height or the subscapular skinfold.

The finding of a significant association between systolic blood pressure and serum uric acid level in our 1963 cross section examination¹² is confirmed and somewhat clarified by our present finding of a significant association between uric acid and incidence of hypertension. Previous report

*This association is with the actual number of people living together but is not related to the crowding index (No. 15—number of persons per room).

the development of hypertensive levels is more probable for those with blood pressures at the upper boundary of normal and less probable for those with pressures much below this. In the present paper we have established some associations between certain variables and subsequent hypertension incidence. In later reports from this study using multivariate methods we hope to explore whether the variables we have identified contribute to excess risk only through their association with high line pressure or whether there is a significant association after an adjustment for high line pressure is made. In any event we are presently only at the beginning of our understanding of the relationship between hypertension incidence and the variables considered herein.

Summary

In a study of male Israeli civil service workers five year incidence rates of hypertension (using the WHO definition) were found to increase with age and were higher for European born subjects. Data are presented in support of a hypothesis that the size of the family group living together is inversely related to the risk of developing hypertension. Other factors found associated (at $p < 0.01$ level) with hypertension incidence (all positively) were weight/height ratio, skinfolds, serum uric acid, pulse rate, cigarette smoking and prolongation and suppression of feelings following conflicts in certain life situations. Other associated variables between the <0.01 and <0.05 levels are recorded and the fact is stressed that we are only at the beginning of an understanding of factors associated with hypertension incidence.

Our sincere thanks go to Prof J J Green for much of the thinking and the development of the questionnaire related to the psycho-social variables used in this study.

REFERENCES

- Kagan A, Gordon T, Kannel W B et al. Blood pressure and its relation to coronary heart disease in the Framingham Study. *Hypertension* Am J Clin Hypertens 1979; Vol VII.
- Green J J, Medalie J H, Neufeld H N et al. An epidemiologic investigation of hypertension and ischemic heart disease within a defined segment of the adult male population of Israel. *Isr J Med Sci* 4:177, 1968.
- Arterial hypertension and ischemic heart disease. Preventive aspects. Technical Report Series No 231 Geneva: WHO 1967.
- Medalie J H, Ris F, Neufeld H N et al. Some practical problems of observer variation in a large survey in Cardiology—Current topics and progress. New York/London 1970. Academic Press Inc. pp 100-104.
- Medalie J H, Neufeld H N, Ris F et al. Variations in prevalence of ischemic heart disease in defined segments of the male population of Israel. *Isr J Med Sci* 4:175, 1968.
- Kahn H A, Medalie J H, Neufeld H N et al. Serum cholesterol: its distribution and association with dietary and other variables in a survey of 10,000 men. *Isr J Med Sci* 11:117, 1969.
- Kahn H A, Herman J B, Medalie J H et al. Factors related to diabetes incidence: A multivariate analysis of two years observation on 10,000 men. *J Chronic Dis* 23:617, 1971.
- Bilgory M, Medalie J H, Smith H et al. The development of a dietary questionnaire for an ischemic heart disease survey. *Isr J Med Sci* 1:195, 1968.
- Schweitzer M D, Geering F R and Perera G A. Family studies of hypertension: Their contribution to the understanding of genetic factors. In Stamler J, Stamler R and Lullman T N, editors. The epidemiology of hypertension. Proceedings of an international symposium. New York and London 1967. Grune & Stratton Inc. pp 28-37.
- Schweitzer M D, Geering F R and Perera G A. The epidemiology of primary hypertension: present status. *J Chronic Dis* 18:817, 1965.
- Bilgory M and Lilkhei C W. Treatment of hypertension with an implantable electronic device. *JAMA* 191:647, 1965.
- Medalie J H, Kahn H A, Neufeld H N et al. Myocardial infarction among 10,000 adult males over a 5 year period: I. Prevalence, incidence and mortality experience. *J Chronic Dis* (in press).
- Sive P H, Medalie J H, Kahn H A et al. Distribution and multiple regression analysis of blood pressure in 10,000 Israeli men. *Am J Epidemiol* 93:317, 1971.
- Dunn J I, Ipsen J, Elsom H O et al. Risk factors in coronary artery disease: hypertension and diabetes. *Am J Med Sci* 2:91309, 1970.
- Kannel W B, Brand N, Skinner J J et al. The relation of adiposity to blood pressure and development of hypertension—The Framingham Study. *Ann Intern Med* 67:48, 1967.
- Andros D. Studies on the epidemiology of hypertension in Poland. In Stamler J, Stamler R and Lullman T N, editors. The epidemiology of hypertension. Proceedings of an international symposium. New York and London 1967. Grune & Stratton Inc. pp 87-96.
- Levy R L, Hillman C C, Stroud W D et al. Transient hypertension: its significance in

strate this.¹⁻³ In our initial survey we adopted the procedure of asking whether the subject had presently or in the past, any serious problems in a number of life areas and how he had responded to them. This in essence defines a category which is resultant of the interaction and interrelation between the personality and the socio-cultural situation without at this stage trying to differentiate the effects of each. In addition we developed an anxiety index based on the sum of the answers to a number of questions.

Leaving out of the discussion at this stage the psychosocial aspects of biological variables like cholesterol, uric acid, weight, and so on, significant associations were found with six psychosocial variables. Of these, four of them 'hurt by superior (brood)', 'hurt by superior (restrain from retaliation)', 'hurt by co-workers (brood)', and 'conflict with wife (help to self)' have a common denominator in that they represent a conflict situation with the subject restraining or repressing his feelings within himself in line with parts of the hypotheses as set out by various psychiatrists and others.^{39,40} At this stage we have no evidence that this reflects 'an inability to utilize previously socially sanctioned patterns of behavior,' as suggested.⁴¹

This present paper is limited to the relationship between hypertension incidence and various single variables of interest with the investigation of multivariate relationships to be reported later. However, because the present findings of significant relationship include cigarette smoking, some manifestations of psychic tension, and the number of persons living together, and because it is not unreasonable to suppose that tense people may smoke heavily and be loners, we have investigated the correlation of these variables in our data. For the present, it seems as if each of the three variables cited above is in fact independently related to hypertension incidence. However, more intensive and precise multivariate investigations are in process and will be reported at a later date.

With respect to those variables that we found significantly associated with hypertension incidence at the 0.05 level, we note that the negative relationship with education has been previously reported in cross-

sectional studies from the Framingham Study⁴ and the National Health Survey.⁵ The positive associations between non-specific T wave and blood pressure level and cholesterol and blood pressure level have been previously reported from Framingham.^{4,6}

A rough over-all comparison of findings between our cross-sectional study of blood pressure in relation to specific variables and the present study shows (for variables included in both studies) (1) five variables with similar relationships to blood pressure level or hypertension incidence: a weight/height ratio, uric acid, pulse rate, and cholesterol; (2) five variables significantly associated with blood pressure in the cross-sectional study but not with hypertension incidence: myocardial infarction, anemia, anxiety index, diabetes, and peptic ulcer history (negative); (3) three variables significantly associated with hypertension incidence but not with cross-sectional blood pressure values: number of persons living together, years in the country, and education; and (4) one variable significantly associated with blood pressure level in the cross-sectional study (negative association) and significantly associated with hypertension incidence in the present study (positive association): cigarette smoking.

This is not an appropriate place to discuss in depth the comparative findings with respect to the same variables: prevalence (cross-sectional) and incidence studies, but a few remarks may be appropriate. (1) Of the nine associations found in the incidence study, five were also identified in the prevalence study. (2) The associations found in the cross-sectional analysis are mostly with morbid conditions. (3) The distortion potential in a cross-sectional prevalence study is great enough to invert an association from which in fact is probably positive to a finding of negative.

We are aware of the fact that in relation to future development of hypertension we may in effect be doing no more than relating these variables to blood pressure levels within the population defined to be at risk of hypertension. This follows since among those at risk it is evident that

Interrelationship of hemodynamic alterations of valvular heart disease and renal function influences on renal sodium reabsorption

George A Porter MD*

Frank F Kloster MD**

J David Bristow MD***

Herbert F Griswold MD****

Portland Ore



Definition of the mechanisms responsible for the abnormal salt and water retention which characterizes congestive heart failure remains a challenging problem to clinical investigators despite the remarkable conceptual advances of the last 30 years. Stimulated by the elegant studies of Starr¹ which led to the formulation of the forward theory of heart failure, Warren and Sterd² demonstrated a diminished urinary excretion of sodium and water in cardiac patients commensurate with edema formation. Their findings were confirmed and extended by Merrill³ and by other investigators^{4,5,6} who showed that renal plasma flow and glomerular filtration rate were reduced in patients with heart failure leading to speculation that the ab-

normal salt and water retention simply reflected a more complete tubular reabsorption of the diminished filtered load of sodium. However, several disparities were reported which could not be easily explained by this proposed mechanism. These included (1) evidence that renal sodium retention occurred in dogs with experimental heart failure before any measurable decrease in glomerular filtration rate was recorded;⁷ (2) the development of heart failure in human subjects with normal glomerular filtration rates^{8,9} and (3) spontaneous or induced diuresis during compensation of heart failure without concomitant improvement in depressed glomerular filtration rate.^{10,11} Despite these inconsistencies, Vander and associates¹² in

From the Department of Medicine, University of Oregon Medical School, Portland, Ore.
This study was supported by Cardiac Research Program, Project C-1, H-06330-10, National Heart Institute.
Submitted for publication May 15, 1970; accepted for publication July 1, 1970.
Reprint requests to George A. Porter, MD, Department of Cardiology, Oregon Medical School, Portland, Ore. 97201.
*Associate Professor of Medicine, Chief of Section of Nephrology, Department of Cardiology, Oregon Medical School, Portland, Ore.
**Associate Professor of Medicine, Director of Cardiac Research, Department of Medicine, University of Oregon Medical School.
***Professor of Medicine, Chairman, Department of Cardiology, University of Oregon Medical School.
****Professor of Medicine, Chief, Division of Cardiology, Oregon Medical School, Department of Medicine, University of Oregon Medical School.
Appreciation is expressed to the many individuals who assisted in the collection of data and to the staff of the Oregon Medical School.
Address reprint requests to Dr. Porter, Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland, Ore. 97201.

- terms of later development of sustained hypertension and cardiovascular renal diseases *JAMA* 126:829 1944
- 18 Stamler J Lindberg H A Berkson D M et al Epidemiological analysis of hypertension and hypertensive disease in the labor force of a Chicago utility company in Skelton F R editor Proceedings of the Council for High Blood Pressure Research American Heart Association 1958 pp 23 50
 - 19 Doyle J T Heshin A S, Hilleboe H, et al Early diagnosis of ischemic heart disease *N Engl J Med* 261 1096 1959
 - 20 Koopferstein S I Schiffman A and Ierthy T J Level of initial blood pressure and subsequent development of essential hypertension *Am J Cardiol* 18 116 1962
 - 21 Merrill W F Some personal factors influencing arterial blood pressure in Stamler J Stamler R and Pullman T N editors The epidemiology of hypertension Proceedings of an international symposium New York and London, 1967 Grune & Stratton Inc pp 60 67
 - 22 Stamler J Berkson D M Lindberg H A et al Socioeconomic factors in the epidemiology of hypertensive disease in Stamler J Stamler R and Pullman T N editors The epidemiology of hypertension Proceedings of an international symposium New York and London 1967, Grune & Stratton Inc pp 289 313
 - 23 Tyler H L Body composition and elevated blood pressure A comment in Stamler J Stamler R and Pullman T N editors The epidemiology of hypertension Proceedings of an international symposium New York and London 1967 Grune & Stratton Inc pp 101 104
 - 24 Dawber T R Kannel W B Kagan A et al Environmental factors in hypertension in Stamler J Stamler R and Pullman T N editors The epidemiology of hypertension Proceedings of an international symposium New York and London 1967 Grune & Stratton Inc pp 255 282
 - 25 Epstein F H and Eckoff R D The epidemiology of high blood pressure—geographic distributions and etiologic factors in Stamler J Stamler R and Pullman T N editors The epidemiology of hypertension Proceedings of an international symposium New York and London 1967 Grune & Stratton Inc pp 155 166
 - 26 Shurtleff D Bivariate correlations among some characteristics of the Framingham Cohort at Exam 2 in The Framingham Study in epidemiological investigation of cardiovascular disease Bethesda Md 1968 National Heart and Lung Institute
 - 27 Pardo V Perez Stable F and Fisher L R Ultrastructural studies in hypertension III Gouty nephropathy *Lab Invest* 18 143 1968
 - 28 Clark T W Lison K O Montgomery F H et al Clinical and biological observations on working men *Arch Environ Health* 19 700 1969
 - 29 Smirk I H Genetic hypertension in rats in Stamler J Stamler R and Pullman T N editors The epidemiology of hypertension Proceedings of an international symposium New York and London 1967 Grune & Stratton Inc pp 39 44
 - 30 Pullman T N in Stamler J Stamler R and Pullman T N editors The epidemiology of hypertension Proceedings of an international symposium New York and London 1967 Grune & Stratton Inc p 449
 - 31 Smoking and Health Report of the Advisory Committee to the Surgeon General of the Public Health Service Public Health Service Publication 1103 U S Government Printing Office 1964
 - 32 Kahn H A The Dorn study of smoking and mortality among U S veterans Report on eight and one-half years of observation in Hienzel W editor Epidemiological approaches to the study of cancer and other chronic diseases National Cancer Institute Monograph 19 1966 pp 1 125
 - 33 Hammond E C Smoking in relation to the death rates of one million men and women in Hienzel W editor Epidemiological approaches to the study of cancer and other chronic diseases National Cancer Institute Monograph 19 1966 pp 127 204
 - 34 Shih V V Environmental factors and hypertension with particular reference to prevalence of hypertension in alcohol addicts and teetotalers in Stamler J Stamler R and Pullman T N editors The epidemiology of hypertension Proceedings of an international symposium New York and London 1967 Grune & Stratton Inc pp 204 216
 - 35 Ostfeld A M and Shekelle K P Psychological variables and blood pressure in Stamler J Stamler R and Pullman T N editors The epidemiology of hypertension Proceedings of an international symposium New York and London 1967 Grune & Stratton Inc pp 321 331
 - 36 Thomas C B The psychological dimension of hypertension in Stamler J Stamler R and Pullman T N editors The epidemiology of hypertension Proceedings of an international symposium New York and London 1967 Grune & Stratton Inc pp 332 339
 - 37 Gordon T and Devine B Hypertension and hypertensive heart disease in adults Public Health Service Publication No 1000 Series 11 No 13 U S Dept of Health Education and Welfare 1966
 - 38 Scotch N A and Geiger H J The epidemiology of essential hypertension A review with special attention to psychological and cultural factors *J Chronic Dis* 16:1183 1964
 - 39 Alexander I Emotional factors in essential hypertension *Psychosom Med* 1:143 1939
 - 40 Suhl I H Mortality in cases of essential hypertension *Psychosom Med* 1:153 1939
 - 41 Henry J I and Cyril J C Psychological factors in essential hypertension, *Am J Epidemiol* 90:171 1969

Table I Clinical summary of 19 patients studied during cardiac catheterization

No of patients	Sex		Diagnosis	Functional class	Average age (yr)
	M	F			
10			Mitral stenosis and/or insufficiency		37.3 ± 2.9
3			Aortic stenosis and/or insufficiency		
4			Mixed mitral and aortic valve lesions		
1			Osium primum defect		
1			Left atrial myxoma		
5				Class I	
6				Class II	
8				Class III	
3	16				

Accepted by the American Heart Association for publication.

for mixed venous blood sampling. Systemic arterial blood samples were obtained from an indwelling polyethylene catheter placed percutaneously in the left brachial artery. A cardiac catheter with a preformed curved tip was inserted percutaneously in the right femoral vein and the catheter tip was positioned in the right renal vein for blood sampling. Urine specimens were obtained from an indwelling urethral catheter. Inulin and paraaminohippuric acid (PAH) clearance were measured using a constant infusion technique. Priming doses of PAH (0.03 ml of 20 per cent IAH per kilogram of body weight) and of Inulin (0.5 ml of 10 per cent Inulin per kilogram of body weight) were given initially; these were followed by a constant intravenous infusion of a solution containing 50 ml of 10 per cent Inulin and 10 ml of 20 per cent IAH in 500 ml of 5 per cent dextrose in water delivered by an Amedeco pump at a rate of 3 ml per minute. At this infusion rate the plasma concentration of PAH remained below 5 mg per cent in all patients. The infusion was continued for at least 45 minutes before the study period to allow establishment of an equilibrium state dur-

ing this time catheters were inserted as indicated above. The patient was then allowed to enter a resting state and urine was collected during two sampling periods of 20 minutes each. The urinary bladder was irrigated with sterile distilled water and emptied at the beginning of the first collection period, then emptied and irrigated with a known volume of distilled water at the end of each collection period to insure accurate sampling. Brachial arterial and renal venous blood samples were drawn at the beginning and end of each collection period. Cardiac output was measured by the Fick method at the midpoint of the first collection period and by the radioisotope dilution technique with precordial detection midway through the second period. Intravascular pressures were recorded at both times. Satisfactory positioning of the catheter in the renal vein was verified at the beginning and end of the study by injection of a small amount of radiographic contrast material and by oxymetry of renal vein and inferior vena cava blood samples demonstrating high oxygen saturation of the former.

The methods used to analyze the PAH

1958 rejuvenated interest in the abnormal filtration fraction which characterizes the renal perfusion/filtration adjustment in heart failure.¹² They suggested that blood perfusing the proximal tubule in congestive heart failure had a higher plasma protein concentration because of the increased filtration fraction, resulting in an increased colloid osmotic pressure favoring passive sodium and water reabsorption from the proximal tubule into the peritubular capillary network.

The lack of a consistent relationship between filtered load of sodium and diminished urinary excretion prompted other investigators to search for alternate or supplementary factors which might operate independently or in concert with altered renal perfusion/filtration to cause abnormal salt and water retention. Excretion of aldosterone, a potent endogenous mineralocorticoid, was found to be increased in patients with congestive heart failure suggesting the possibility that the increased tubular reabsorption of sodium present in heart failure may be the result of increased aldosterone activity.¹³ Sufficient data have accumulated to recognize aldosterone overproduction as a significant factor both in perpetuating and in augmenting the pathologic sodium retention of heart failure.^{14,15} However, the absence of edema in patients with primary aldosteronism and the induction of experimental heart failure in adrenalectomized dogs maintained with minimally effective concentrations of exogenous mineralocorticoid replacement¹⁶ precluded increased aldosterone production as the primary salt retaining mechanism responsible for sodium retention in congestive heart failure.

Theories concerning renal regulation of sodium excretion continued to be dominated by consideration of altered filtration rate and aldosterone activity until the early 1960s when two independent observations expanded the number of factors known to modify renal sodium excretion. The first was the finding by deWardner and associates¹⁷ that a sodium diuresis could be induced in dogs despite a severe reduction in glomerular filtration rate and in the presence of excess exogenous mineralocorticoid by the infusion of hypotonic saline. Confirmation of this discovery

by Levinsky and Lalone¹⁸ initiated the search for a "third" factor responsible for the regulation of proximal tubular sodium reabsorption. Findings in support of the regulatory mechanism being humoral in origin¹⁹ and/or physical in character²⁰ have been reported to explain the edema associated with rapid expansion of the extracellular space. The second major contribution was the report by Berger²¹ demonstrating a redistribution of intrarenal blood flow in dogs with experimental heart failure. Using an inert radioactive gas technique he found intrarenal flow to be directed away from superficial cortical nephrons which do not conserve sodium as avidly as the deep cortical and juxtamedullary nephrons to which blood flow was increased in heart failure. These observations have stimulated a reappraisal of the pathophysiological mechanisms responsible for salt and water retention of heart failure. In the following study we have examined the influence of the systemic and renal hemodynamic alterations of heart failure on renal tubular sodium reabsorption.

Methods

Nineteen patients were studied during routine diagnostic cardiac catheterization and were selected to include a spectrum of severity of heart disease. Patient data are tabulated in Table I. Seventeen individuals had valvular heart disease, one had aortic stenosis, one had aortic regurgitation, one had a mitral regurgitation, and one had a left atrial myxoma. Applying the New York Heart Association Classification at the time of study, five patients were in Functional Class I, six were in Class II, and eight were in Class III. All patients were free of overt evidence of heart failure when studied although all of those in Class III and most of those in Class II had previously demonstrated pulmonary and/or systemic venous congestion. Thirteen patients were taking digitalis at the time of study and eight were following a sodium restrictive diet of 2 Gm or less per day. Five patients had been taking thiazide diuretics prior to hospitalization but these were discontinued at least 2 days prior to study.

Right heart catheterization was carried out by standard techniques from a right antecubital cutdown with positioning of the catheter tip in the pulmonary artery.

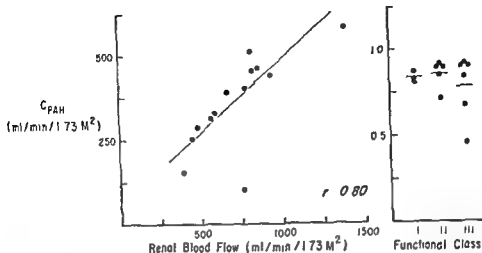


Fig. 2 Correlation plot between para aminohippurate clearance (C_{PAH}) and renal blood flow constructed similar to Fig. 1. The right hand graph compares the renal extraction ratio of PAH (ordinate) to the functional cardiac class. The horizontal lines represent the mean values for each group of solid circles.

of sodium ($T_N +$) was obtained as the difference between filtered sodium and total urinary sodium ($I_N - U_N$) expressed as mEq/min.

Results

Comparison of systemic hemodynamic parameters of patients. Four hemodynamic variables were compared to cardiac index, the classical measure of systemic hemodynamic function. These included (1) mean left atrial pressure, (2) mean pulmonary artery pressure, (3) arteriovenous oxygen difference and (4) total blood volume. Fig. 1 depicts the inverse correlation between cardiac index and mean left atrial pressure; the correlation coefficient (r) of -0.78 was highly significant. A similar relationship existed with mean pulmonary artery pressure ($r = -0.68$). As expected because of the interdependence of these variables, a significant inverse correlation was evident between arteriovenous oxygen difference and cardiac index ($r = -0.82$). No consistent relationship could be demonstrated between cardiac index and total blood volume ($r = -0.30$). Since the determinations of cardiac index and mean left atrial pressure are not interdependent, we chose them as hemodynamic parameters for comparison with the measurements of renal hemodynamics.

Extraction of PAH. It has been suggested¹ that the extraction of para

aminohippurate by the kidney declines in patients with congestive heart failure, thus distorting the expected linear relationship between renal blood flow and C_{PAH} . In 15 of the 19 patients studied, it was possible to obtain a technically satisfactory renal vein blood sample for PAH analysis. To determine if clearance of PAH was a true reflection of renal blood flow, the clearance of PAH was compared to renal blood flow corrected for both hematocrit and extraction ratio of PAH. An excellent correlation existed between these two parameters (Fig. 2) and no consistent relationship between E_{PAH} and cardiac functional classification was evident. We have concluded that C_{PAH} is a reliable estimate of renal blood flow under the conditions in which our patients were studied.

Comparison of systemic and renal hemodynamics. Relationships between systemic hemodynamic variables and C_{PAH} are shown in Fig. 3. In confirmation of the recent report of Kinoshita² there was a significant direct correlation between cardiac index and PAH clearance ($r = 0.75$). As would be expected from the hemodynamic relationships above, C_{PAH} correlated inversely with mean left atrial pressure and had no relationship to total blood volume.

Filtration fraction. The portion of renal plasma flow filtered by the glomerulus had

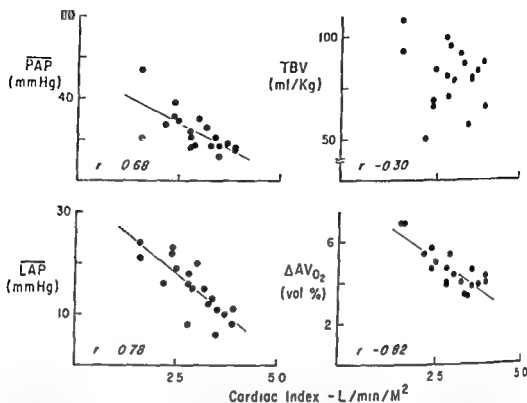


FIG. 1 Four correlation plots comparing cardiac index on the abscissa to various hemodynamic parameters on the ordinate. \overline{LAP} = mean left atrial pressure, \overline{PAP} = mean pulmonary artery pressure, ΔAVO_2 = arteriovenous oxygen difference, TBV = total blood volume. Regression lines were obtained by the method of least squares and r represents the derived correlation coefficient (see reference No. 41).

and Inulin content of serum and urine samples were identical to those previously reported by this laboratory. Plasma clearance of PAH was calculated from the formula:

$$C_{PAH} = \frac{U_{PAH} \times V}{P_{PAH}} \quad (1)$$

where U_{PAH} and P_{PAH} represent the urine and plasma concentrations and V represents the volume of urine. The renal extraction of PAH was calculated from the formula:

$$E = \frac{A_{PAH} - V_{PAH}}{A_{PAH}} \times 100 \quad (2)$$

where A_{PAH} and V_{PAH} are the concentrations of PAH in the systemic arterial and renal venous blood. Renal blood flow is calculated from the formula:

$$RBF = \frac{C_{PAH}}{E_{PAH}} \times \frac{100}{1 - \text{hematocrit}} \quad (3)$$

Inulin clearance was calculated as with the PAH clearance formula. The brachial ar-

terial and mixed venous blood samples for Fick cardiac output calculation were analyzed for oxygen content by the Van Slyke Neill method and the expired gas sample was analyzed for oxygen content by the Scholander technique. Cardiac output determination by the radioisotope dilution technique was performed as described previously with injection of $1\mu Ci$ of ^{125}I labeled human serum albumin in the right atrium.² Intravascular pressures were measured with Statham P ^{23}Cb transducers and recorded on a Sanborn photographic recorder.

Renal vascular resistance (RVR) was calculated using the following formula⁴¹

$$RVR = \frac{BP}{RBF - RAP} \quad (4)$$

where \overline{BP} is mean arterial blood pressure, RAP is right atrial blood pressure, and RBF is renal blood flow corrected for PAH extraction. Vascular resistance was expressed in arbitrary units. Renal oxygen consumption was derived as the product of renal blood flow and renal arteriovenous oxygen difference; the result expressed as ml/min/1.73 M 2 . Tubular reabsorption

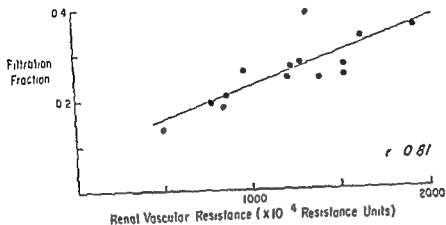


Fig. 5 Correlation plot of filtration fraction (FF) versus renal vascular resistance. Constructed similar to Fig. 1

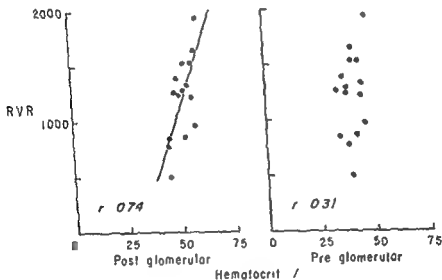


Fig. 6 Correlation plot of renal vascular resistance (RVR) compared to pre and postglomerular hematocrits. Constructed similar to Fig. 1

patients but the individual values did not correlate with the severity of the impaired cardiac output (Fig. 7).

In an attempt to appraise any renal adaptation to decreased cardiac output the renal arteriovenous oxygen difference was compared to the cardiac index. A highly significant inverse correlation resulted which was also true when renal blood flow was compared to cardiac output (Fig. 8). Thus it would appear that as cardiac output diminished renal blood flow followed at an equal rate and the renal arteriovenous oxygen difference increased in a manner similar to muscle and other tissues.

Comparison between hemodynamic alterations and renal tubular sodium reabsorption. It has been suggested that the increased filtration fraction associated with the diminished renal blood flow in patients with heart failure maintains the filtered load of sodium resulting in a relative enhancement of tubular sodium reabsorption. In an attempt to elucidate a pathophysiologic mechanism consonant with increased filtration fraction and sodium retention we examined glomerulo-tubular balance in our patients. When the filtered load of sodium was plotted against net tubular reabsorption of sodium for all 19 patients a near

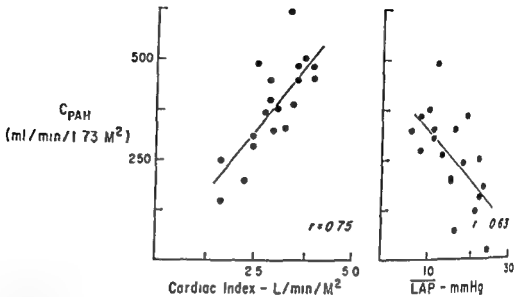


Fig. 3 Correlation plot of PAH clearance (ordinate) compared to either cardiac index or mean left atrial pressure (LAP) constructed similar to Fig. 1

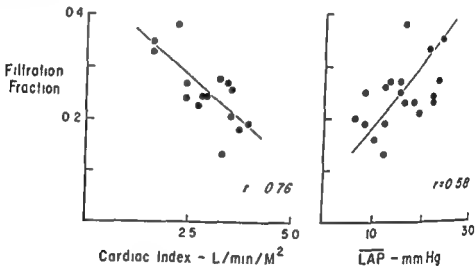
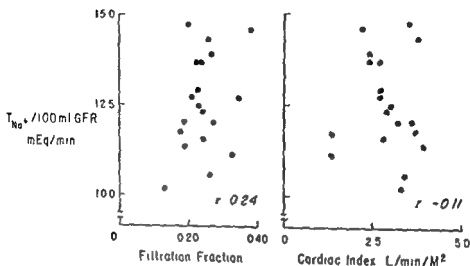


Fig. 4 Correlation plot of filtration fraction (FF) (see text for definition) compared to cardiac index or mean left atrial pressure (LAP) Constructed similar to Fig. 1

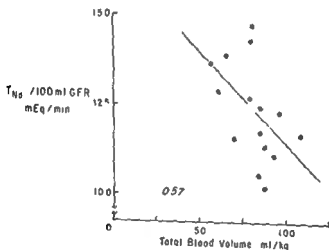
a highly significant inverse correlation with cardiac index as shown in Fig. 4 ($r = 0.76$). Previous authors¹² have considered this renal adaptive mechanism to be responsible for the excess Na^+ retention which is characteristic of congestive heart failure. From the data presented in Fig. 5 it would appear that preservation of the filtration rate in the face of a fall in renal plasma flow occurs through an increase in the afferent or postglomerular arteriolar resistance, since the filtration fraction correlated directly with renal vascular resistance. Possibly contributing to the increased resistance is the postglomerular hemato-

crit, which correlated directly with renal vascular resistance (Fig. 6). The possible influence of increased blood viscosity associated with the rising hematocrit on renal vascular resistance has been discussed by Mills.¹⁴

Thus although renal blood flow declines as cardiac index falls there is increased postglomerular vascular resistance which serves to maintain glomerular filtration rate. This change in perfusion/filtration balance is not directly dependent on a diminution in the percent of cardiac output received by the kidneys, since the renal fraction averaged 14.6 per cent for our



9 Correlation plot of normalized tubular sodium reabsorption ($T_{Na^+}/100 \text{ ml GFR}$) and either filtration fraction or cardiac index. Constructed similar to Fig. 1.



10 Correlation plot of normalized tubular sodium reabsorption and total blood volume. Constructed similar to Fig. 1.

actional sodium reabsorption from the proximal tubule is the influence of extracellular volume expansion, the so-called fluid factor. An indirect method for assessing the possible existence of such a modification of tubular sodium reabsorption in our patients is by comparing the normalized tubular reabsorptive rates with simultaneously measured total blood volumes. These data are plotted in Fig. 10 and demonstrate an inverse relationship between the two parameters. Acknowledging that cause and effect cannot be judged from such a correlation plot, these findings support the concept that an alteration

in extracellular fluid volume can induce a systematic change in measured tubular sodium reabsorption.

Comparison of renal oxygen consumption and tubular sodium reabsorption. From various animal studies^{14,15} it has been reported that approximately 30 mEq of sodium are actively reabsorbed for each millimole of oxygen consumed. We also measured net sodium reabsorption—that is, the difference between the sodium actively transported out of the tubular lumen and that which passively diffuses back into the lumen—and we have derived the Na^+/O_2 ratio for each of the patients

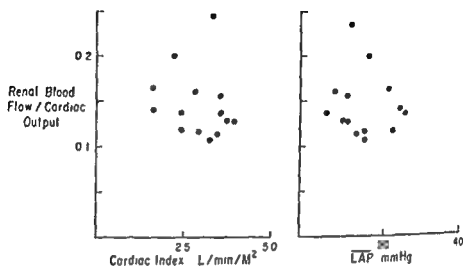


Fig 7 Correlation plot of renal fraction (renal blood flow/cardiac output) compared to either cardiac index or to mean left atrial pressure (LAP). Constructed similar to Fig 1. See text for statistical analysis.

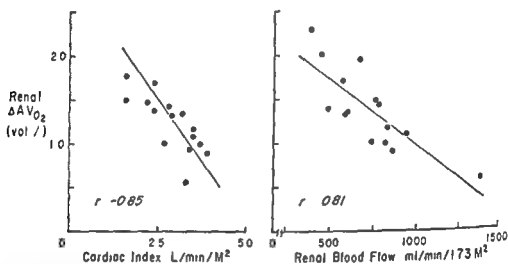


Fig 8 Correlation plot of renal arteriovenous oxygen difference ($\Delta V O_2$) compared to cardiac index or to renal blood flow. Constructed similar to Fig 1.

perfect correlation resulted a finding compatible with intact glomerulo tubular balance. However since only a minute imbalance would be required to produce appreciable sodium retention this classical technique for expressing glomerulo tubular balance is probably too insensitive to detect the changes which are postulated to occur in congestive heart failure.

As an alternate means of detecting a unique enhancement of tubular sodium reabsorption at increased filtration fractions each individual tubular reabsorptive rate was standardized to a common load of 100 ml glomerular filtration rate (GFR) and plotted with respect to the derived filtration fraction. These data are shown on Fig 9. In this graph, the normalized tubu-

lar reabsorption of sodium appears in the ordinate while either the cardiac output or filtration fraction are shown on the abscissa. If in association with an increasing filtration fraction tubular reabsorption of sodium were to increase a linear relationship would be predicted. As a corollary if cardiac failure as manifested by a decreased cardiac output were associated with enhanced Na^+ reabsorption then an inverse relationship would exist for cardiac index. As can be seen from Fig 9, no significant correlation was present for either filtration fraction or cardiac index. This finding supports the conclusion that glomerulo tubular balance is intact in patients with compensated congestive heart failure.

Another factor which will modify the

sodium retention both through intrarenal mechanisms that enhance sodium reabsorption and through the secondary effects of the renin-angiotensin system to stimulate the secretion of aldosterone. Our findings (Figs 5 and 6) are compatible with such a postulated mechanism. Efferent arterio-vascular constriction would result in a lowered capillary hydrostatic pressure per-
fusing the proximal tubule thus exerting less impedance to sodium reabsorption according to the standing gradient model for sodium transport proposed by Diamond.²² Furthermore plasma oncotic pressure would rise at an equal rate with the post-glomerular hematocrit providing an additional driving force for increased interstitial fluid uptake by the peritubular capillaries. An additional contributing factor would be the slower blood flow in the peritubular capillary network which would provide more time for equilibration thus allowing these physical forces to exert a more complete effect.

A classical plot of filtered load versus tubular reabsorption failed to show any distortion of glomerular tubular balance with regard to renal sodium handling in our patients with heart failure. Obviously minute changes in net sodium reabsorption might be obscured by this type of analysis and still could account for the abnormal salt and water retention of heart failure. To search more critically for the unique tubular enhancement of sodium reabsorption in heart failure postulated above tubular sodium reabsorption for each patient studied was standardized to a common filtered load and compared to filtration fraction and cardiac index. Since the serum sodium for 17 of the 19 patients was within the normal range for our laboratory and showed no correlation with either filtration fraction or cardiac index only CFR represented a significant variable and it was eliminated by the technique of normalization employed. If associated with an increased filtration fraction elevated plasma oncotic pressure and reduced capillary hydrostatic pressure were primary determinants of tubular sodium reabsorption then a direct relationship with filtration fraction would be expected which was not the case (Fig 9). Conversely if systemic blood flow were to influence T_{Na} an inverse corre-

lation would be anticipated and this finding was also absent. These findings support the conclusion that no gross distortion of glomerulo-tubular balance exists in patients with compensated congestive heart failure. Further evidence supporting preservation of glomerulo-tubular balance is the appropriate response of renal tubular sodium reabsorption to volume expansion as seen in the results presented in Fig 10. The inverse correlation between normalized T_{Na} and total blood volume would be predicted from the reported effects of extracellular volume expansion on proximal tubular sodium reabsorption in both rats and dogs.^{11, 15, 16} However, since we measured net tubular sodium reabsorption without discriminating between proximal and distal tubular uptake the magnitude of the volume-induced proximal tubular depression would be obscured by this technique of measurement.

At first glance these findings seem to contradict our original suggestion that the sodium retention of cardiac failure involves altered tubular function. However it must be emphasized that we measured net tubular sodium reabsorption which represents the difference between active transcellular Na^+ transport and passive back-diffusion of sodium into the nephron lumen. A technique which we considered for indirectly evaluating the relative contribution of these two simultaneous processes in man was to determine the moles of sodium reabsorbed per mole of oxygen consumed, the results being expressed as a Na^+/O_2 ratio. Studies of the relationship between tubular reabsorption of sodium and renal oxygen consumption in animals indicate that approximately 30 equivalents of sodium are actively reabsorbed per mole of oxygen consumed.^{23, 24} Furthermore using pharmacologic blockade of the distal renal tubule of dogs Bjekshus, Aukland, and Kul²⁵ concluded that the Na^+/O_2 ratios for proximal and distal tubular segments were similar. However the Na^+/O_2 ratio was observed to fall when mannitol diuresis was superimposed on distal tubular blockade a finding which was best explained by enhanced passive back diffusion of sodium.²⁷ Our findings of a direct correlation between the Na^+/O_2 ratio and the glomerular filtration rate and an inverse

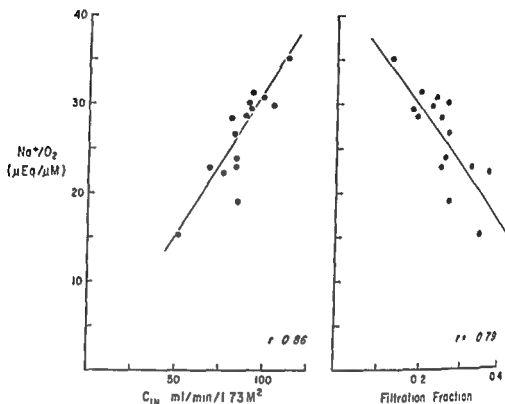


Fig 11 Correlation plot of net sodium reabsorption per mole of oxygen consumed (Na^+/O_2) and glomerular filtration rate (C_{1N}) or filtration fraction. Constructed similar to Fig 1

studied. These data are shown in Fig. 11 where they are compared either to the glomerular filtration rate or to the filtration fraction. As can be seen, a direct correlation was present between C_{1N} and Na^+/O_2 , while an inverse relationship exists between filtration fraction and Na^+/O_2 .

Discussion

Evidence regarding increased tubular sodium reabsorption as the intrinsic renal defect in both experimental and clinical heart failure has been recently summarized by Genest and colleagues.⁹ Salient points of this review include (1) the impaired excretion of a hypertonic saline load in dogs with experimental heart failure when compared to the response in normal controls, (2) the finding of glomerular filtration rates that are within normal limits in patients with frank congestive heart failure and the observation that filtration rate decreased in some patients during decongestive treatment without impairing the response to diuretic drugs, (3) evidence of increased endogenous mineralocorticoid activity in patients with heart failure, and (4) absence of overt sodium retention in

patients with renal artery stenosis despite marked reductions in both glomerular filtration rate and renal blood flow. However, a unified hypothesis regarding the mechanism responsible for this abnormal tubular retention has eluded investigators. Evidence favoring an increased tubular sodium reabsorption occurring in both the proximal^{10,11} and distal tubule¹² further complicates definition of a pathophysiologic scheme consonant with divergent views. We have examined the relationship between systemic and renal hemodynamics present in a group of patients with valvular heart disease as they influence tubular reabsorption of sodium.

The preservation of a normal or near normal glomerular filtration rate in the face of a declining renal blood flow has been the basis for many explanations of the abnormal sodium retention of heart failure. However, extrapolating from the observations reported by Friedler and co-workers¹³ that pharmacologically induced renal vasodilatation leads to a sodium diuresis in animals with experimental edema, Easley and Daugharty¹⁴ suggest that "increased renal vascular resistance could result in

tation encountered in chronic anemia. Evidence supporting intact glomerulo proximal tubular balance is presented along with a comparison of oxygen consumption per mole of sodium reabsorbed. These data are compatible with either redistribution of intrarenal blood flow or with alteration of renal tubular sodium reabsorption downstream from the proximal portion of the nephron as the pathophysiologic explanation of the abnormal sodium retention of heart failure.

REFERENCES

- 1 Starr I Role of the static blood pressure in abnormal increments of venous pressure especially in heart failure II Clinical and experimental studies Am J Med Sci 199:40 1940
- 2 Warren J V and Stead E A Fluid dynamics in chronic congestive heart failure An interpretation of the mechanisms producing the edema increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure Arch Intern Med 73:138 1944
- 3 Merrill A J Edema and decreased renal blood flow in patients with chronic congestive heart failure Evidence of forward failure as the primary cause of edema J Clin Invest 23:389 1946
- 4 Mokotoff R Ross G and Lester L Renal plasma flow and sodium reabsorption and excretion in congestive failure J Clin Invest 47:1 1948
- 5 Blegen E Kidney function in heart failure Scand J Clin Lab Invest 1:278 1949
- 6 Newman E V Function of the kidney and metabolic changes in cardiac failure Am J Med 2:490 1947
- 7 Burger A C Yates F E and Tudolph A M Renal hemodynamics and sodium excretion in dogs with graded valvular damage and in congestive failure Am J Physiol 100:601 1951
- 8 Briggs A P Fowell D M Hamilton W F Remington J W Wheeler A C and Winlow J W Renal and circulatory factors in the edema formation of congestive heart failure J Clin Invest 27:810 1948
- 9 Heller B L and Jacobson W L Renal hemodynamics in heart disease Acta HEART 7:9 1950
- 10 Davis C E The effects of treatment on the renal circulation in heart failure Lancet 11:1057 1951
- 11 Wekstein J Buchter H and Eliasch H Correlation between renal dynamics cardiac output and right heart pressure in mitral valve disease and heart failure J Clin Lab Invest 41:15 1957
- 12 Van der A J Malviu R L Wilde W S and Sullivan L P Editorial Examination of salt and water retention in congestive heart failure Am J Med Sci 197:1958
- 13 Sanders I L and Melby J C Aldosterone and the edema of congestive heart failure Arch Intern Med 113:331 1964
- 14 Cox J R Davies Jones G A B and Leonard I J Sodium content and urinary aldosterone excretion in patients with congestive heart failure before treatment and comparison with normal subjects undergoing salt restriction Clin Sci 26:177 1964
- 15 Davis J O Holman J E Carpenter C C J Urquhart J and Higgins J T Jr An extra adrenal factor essential for chronic renal sodium retention in presence of increased sodium retaining hormone Circ Res 14:117 1964
- 16 Davis J O Howell D S and Hyatt R F Sodium excretion in adrenalectomized dogs with chronic cardiac failure produced by pulmonary artery constriction Am J Physiol 203:763 1953
- 17 deWardener H E Mills I H Clapham W F and Hayter C J Studies on the efferent mechanism of the sodium diuresis which follows the administration of intravenous saline in the dog Clin Sci 21:749 1961
- 18 Levinsky V G and Lalone P C The mechanism of sodium diuresis after saline infusion in the dog J Clin Invest 42:1261 1963
- 19 Hector F C Jr Sellman J C Martinez Maldonado M and Seldin D W The mechanism of suppression of proximal tubular reabsorption by saline infusion J Clin Invest 46:47 1967
- 20 Earley L E Martino J A and Friedler R M Factors affecting sodium reabsorption by the proximal tubule as determined during blockade of distal sodium reabsorption J Clin Invest 40:1668 1966
- 21 Burger A C Renal hemodynamic factors in congestive heart failure Ann N Y Acad Sci 139:776 1966
- 22 Porter G A Kloster F E and Britton J D Sequential effect of angiographic contrast agent on canine renal and systemic hemodynamics Am HEART J 81:90 1971
- 23 Kloster F E Britton J D Starr A McCord C W and Griswold H E Renal cardiac output and blood volume studies following cardiac valve replacement Circulation 33:528 1966
- 24 Gomori P Nagy Z Jakab I and Vajda V Problems in the measuring of renal circulation Acta Physiol Hung 19:79 1961
- 25 Kurohita M Studies on cardiac output to blood volume and renal circulation in chronic congestive heart failure Jap Circ J 32:749 1968
- 26 Mills I H Renal regulation of sodium excretion Ann Rev Med 21:75 1970
- 27 Lassen V Munk O and Thaysen J H Oxygen consumption and sodium reabsorption in the kidney Acta Physiol Scand 51:371 1961
- 28 Kjeldsen J Auland K and Juul F Oxygen cost of sodium reabsorption in proximal and

relationship to the filtration fraction suggest at least two interpretations. The most obvious one is that with chronic heart failure a smaller percentage of renal energy derived from oxidative metabolism is involved in active tubular sodium reabsorption thus disturbing the expected close correlation between $\dot{V}O_2$ and active sodium transport.²⁷ However, these findings are also compatible with an increased passive back diffusion of sodium into the tubular lumen since a reduced flow rate per nephron would provide more time for equilibration. Mechanistic increased back diffusion could occur either along intracellular channels which have been demonstrated between the proximal tubular cells of dogs and rats^{32,33} or by a preferential redistribution of intrarenal blood flow to juxta medullary nephrons. The latter possess longer descending loops of Henle which provide a greater surface area for passive reentry of sodium as well as the more favorable gradient which exists in the medullary area.¹

Support for both of these speculated mechanisms is available from animal studies. Martino and Earley³⁴ using the intact dog kidney, presented evidence supporting the concept of proximal tubular sodium reabsorption being regulated by physical factors. Alternatively, Burger¹ has reported that blood flow to the outer cortex of the kidney is reduced following the induction of experimental heart failure in dogs. Combined with previous observations that dogs undergoing a saline diuresis preferentially redistribute blood flow to the renal cortical region, Burger concludes that the nephron population of the kidney has a spectrum of sodium retaining characteristics and the magnitude of sodium excretion is dependent upon the relative distribution of blood flow to these various nephrons. Since cortical nephrons are less effective sodium reabsorbers than deeper nephrons, the redistribution of intrarenal blood flow away from superficial nephrons impairs the excretion of excess sodium. Our data do not allow a choice between these alternatives.

Finally, the inverse correlation between cardiac output and renal O_2 extraction evident in Fig. 8 suggests an adaptation similar to that reported with anemia. Using

dogs made chronically anemic by bleed³⁵ and by Apcer, Liebow, and Roberts⁴⁰ have shown that the renal adaptation to the hypoxia of anemia is not through increased renal blood flow by vasodilatation but rather occurs from the widening of the arteriovenous oxygen difference due to an enhanced tissue PO_2 gradient. It is of interest that associated with the reduced filtration fraction which they observed (a result of a disproportionate decrease in glomerular filtration rate), the fractional tubular reabsorption of sodium increased. These investigators concluded that the anemic animal retains normal renal function by reducing the filtered load of sodium and by more efficient O_2 extraction both factors diminishing the work requirement of the organ. It is possible that a similar renal adaptive mechanism may operate in chronic heart failure. However, instead of this mechanism representing a primary adaptation, this process in CHF could be initiated by increased cellular O_2 consumption resulting from increased tubular sodium reabsorption in an attempt to increase the vascular volume and thus improve cardiac filling pressure and raise cardiac output. The lowered intracellular PO_2 would raise the gradient between cell and capillary and increase the oxygen diffusion rate culminating in increased renal oxygen extraction as measured by AV difference. Thus despite the pathologic character of the increased sodium reabsorption in heart failure, oxidative metabolism would not be rate limiting and thus would provide protection in conditions where sodium retention is critical to survival of the organism.

Summary

The correlations between systemic hemodynamic parameters—i.e., cardiac index, mean left atrial pressure, total blood volume, and renal blood flow corrected for PAH extraction ratio—are reported for 14 patients with compensated congestive heart failure. In addition, simultaneous measurements of net tubular sodium reabsorption and renal oxygen consumption were compared to both systemic and renal hemodynamic measurements. The significant inverse correlation between cardiac index and renal blood flow and renal arteriovenous oxygen difference resembles the renal adap-

Experimental and laboratory reports

Comparison of the effects of two anesthetic agents on the production of hypoxic pulmonary hypertension in dogs

Armando Susmano MD*

Mitchell Passerow MA**

Richard A Carleton MD***

Chicago Ill

Hypoxia has been used to induce transient pulmonary hypertension in man^{1,2} and in experimental animals.^{3,4} Studies in dogs have been rendered difficult because a pulmonary arterial pressor response to the inhalation of low concentrations of oxygen does not occur in some dogs. This variability has led to the designation of two groups of dogs identified as reactors and nonreactors.⁵ This difference in reactivity has been variably attributed to the sensitivity of individual dogs to the depth of anesthesia, to an influence of the anesthetic agents on the vasomotor centers¹⁰ and to a poorly understood time lag between the onset of anesthesia and the exposure to the low oxygen concentration.¹¹ The latter study suggested that all dogs became reactors if approximately eight hours elapsed between the onset of anesthesia and the hypoxic stimulus.

In the course of studies conducted in animals alternately breathing room air and gas with an inspired oxygen concentration

of 8 per cent it became apparent that our studies also were doomed to uncertainty because of the existence of reactors and nonreactors. This initial group of dogs had been anesthetized with sodium pentobarbital as has been the case in prior studies with animals.^{3,4} The increasing evidence that pentobarbital anesthesia profoundly modifies many cardiovascular functions^{12,13} led us to hypothesize that the anesthetic was the source of the variability. We then conducted a comparative experimental trial of the effects of hypoxia using dogs anesthetized either with sodium pentobarbital or with a mixture of droperidol and fentanyl.

The pharmacologic actions of droperidol¹⁴ include central nervous system depression manifested by marked reduction in spontaneous motor activity, a loss of responsiveness to normal environmental sounds, minimal respiratory depression, a tendency to sleep with little effect on the cardiovascular system at a dose which produces a sedative or depressant effect.¹⁵

From the Section of Cardiovascular Disease, Department of Medicine, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Ill.

Received for publication Sept. 15, 1971.

Reprint requests to Dr. Richard A. Carleton, Department of Medicine, Presbyterian-St. Luke's Hospital, 1753 W. Chicago Parkway, Chicago, Ill. 60612.

Assistant Professor, Rush Medical College.

**Associate Professor, Rush Medical College.

***Professor, Rush Medical College.

†Fentanyl, MeMol Laboratories, Inc., Fort Washington, Pa.

- distal parts of the nephron *Scand J Clin Lab Invest* 23:307 1969
- 29 Genest J, Granger P, deChamplain J and Boucher K. Endocrine factors in congestive heart failure *Am J Cardiol* 22:35 1968
 - 30 Bell N H, Schedl H P and Birtter I C. An explanation for abnormal water retention and hyposmolality in congestive heart failure *Am J Med* 36:351 1964
 - 31 Gibson D G, Marshall J C and Lockey E. Assessment of proximal tubular sodium reabsorption during water diuresis in patients with heart disease *Br Heart J* 32:399 1970
 - 32 Gill J R. Edema *Ann Rev Med* 21:769 1970
 - 33 Friedler R M, Belleau I J, Martino J A and Earley L E. Hemodynamically induced natriuresis in presence of sodium retention resulting from constriction of thoracic inferior vena cava *J Lab Clin Med* 69:565 1967
 - 34 Earley L E and Daugharty T M. Sodium metabolism *N Engl J Med* 281:72 1969
 - 35 Diamond J M. Standing gradient model of fluid transport in epithelia *Fed Proc* 30:6 1971
 - 36 Hyslett J P, Kasharian M and Epstein I. Changes in proximal and distal tubular reabsorption produced by rapid expansion of extracellular fluid *J Clin Invest* 46:174 1967
 - 37 Kul F, Aukland K and Refsum H E. Renal sodium transport and oxygen consumption *Am J Physiol* 201:511 1961
 - 38 Curran P F and MacIntosh J R. Model system for biological water transport *Nature* 193:347 1962
 - 39 Martino J A and Earley L E. Relationship between intra renal hydrostatic pressure and hemodynamically induced changes in sodium excretion *Circ Res* 23:371 1968
 - 40 Aperia A C, Liebow A A and Robert L E. Renal adaptation to anemia *Circ Res* 22:489 1968
 - 41 Snedecor G W. *Statistical Methods* 13th edition Ames Iowa 1956 Iowa State University Press pg 160

Table 1 Data obtained before and during hypoxia in dogs anesthetized with pentobarbital (Group A) or a droperidol fentanyl mixture (Group B)

	P_{O_2} (mm Hg)	pH	P_{CO_2} (mm Hg)	Cardiac output (L/min)	Heart rate (beats/min)	Mean pulmonary artery pressure (mm Hg)	Mean wedge pressure (mm Hg)
Room air							
Group A							
No.	19	??	21	20	??	??	18
Mean	91	7.34	34.6	4.17	136	15.3	4.4
S.E.	3.1	0.01	1.71	0.36	6.66	1.37	0.85
Group B							
No.	17	18	18	18	18	18	17
Mean	91	7.31	40.5	7.77	93	11.1	3.6
S.E.	1.0	0.01	0.01	1.08	5.84	0.55	0.46
p	N.S.	<0.05	<0.01	<0.01	<0.001	<0.001	N.S.
8 per cent oxygen							
Group A							
No.	8	8	8	20	??	22	16
Mean	34.5	7.49	23.6	4.31	204	17.7	4.6
S.E.	2.2	2.07	1.89	0.36	5.87	1.44	0.87
Group B							
No.	17	18	18	18	18	18	18
Mean	36.5	7.44	27.8	3.0	134	13.7	3.4
S.E.	1.4	0.01	0.99	0.17	10.5	7.7	0.37
p	N.S.	<0.10	<0.05	<0.01	<0.001	<0.07	N.S.

N.S. = not significant

tanyl group while the dogs were breathing room air probably reflecting slight differences in respiratory depression. The mean pulmonary arterial pressures while breathing room air differed significantly with an average value of 15.3 ± 1.3 S.E. mm Hg in those dogs anesthetized with pentobarbital and 9.7 ± 0.5 mm Hg in the dogs anesthetized with droperidol fentanyl. Pulmonary hypertension developed during the first minute of breathing 8 per cent oxygen and reached a stable level by the fifth minute and returned to control levels within two minutes after the dogs again breathed room air.

It is well known that acidosis and hypercapnia induce pulmonary hypertension. From this one might have expected that the droperidol fentanyl group would have had higher initial pulmonary artery pressures than the pentobarbital group. Left atrial pressure, assessed as the pulmonary arterial wedge pressure, did not differ between the two groups. It seems most likely

that the difference in mean pulmonary artery pressure between the two groups reflects the higher cardiac output found in the pentobarbital group. This was tested by calculating the pulmonary vascular resistance levels. These were not different in the two groups with average values of 291 dynes sec cm^{-2} and 280 dynes sec cm^{-2} respectively.

Only 13 of the 22 dogs which received pentobarbital anesthesia developed pulmonary hypertension in response to the 8 per cent oxygen-inhaled gas mixture. Conversely, all 18 dogs which received droperidol fentanyl anesthesia developed a pulmonary pressor response to hypoxia. This qualitative difference in frequency is highly significant ($p = 0.0055$) as calculated by the exact probability method of Fisher.¹⁷ These data indicate that a change in the anesthetic agent abolished the apparent reactor-nonreactor dichotomy among dogs exposed to a hypoxic inhaled gas mixture.

The pharmacologic actions of fentanyl* resemble those of morphine. The duration of action is brief with a half time of 15 to 20 minutes. A mild hypotensive effect and sinus bradycardia usually occur, the latter is immediately antagonized by atropine. The vagus plays a major role in the production of this bradycardia because this action is significantly reduced in bilaterally vagotomized dogs. The mild hypotensive response is not due to a cholinergic or histaminic like effect since it is not blocked by vagotomy, atropine or antihistamines.^{14, 15}

Both droperidol and fentanyl have their own effects without well defined antagonistic or potentiating interactions, except that droperidol enhances the analgesic activity of fentanyl. The combination produces potent analgesia and sedation.

Materials and methods

Forty mongrel dogs of both sexes divided into two consecutive groups, were studied utilizing the same protocol but with different anesthetic agents. The initial 22 animals (weight range 13.4 to 22 kilograms mean 17.7 kilograms) were anesthetized with sodium pentobarbital† administered intravenously in a dose of 30 mg per kilogram. The subsequent 18 dogs (weight range 12.3 to 23.5 kilograms mean, 16.2 kilograms) received a mixture of 20 mg of droperidol and 0.4 mg per cubic centimeter of fentanyl‡ in a dose of 0.3 ml per kilogram. Supplemental doses of 30 mg of pentobarbital or 0.5 to 1.0 cc of droperidol/fentanyl were given as necessary to ensure continued anesthesia. Each dog receiving droperidol/fentanyl also received 0.4 mg of atropine sulfate subcutaneously at the time of droperidol/fentanyl administration. A cuffed endotracheal tube ensured a leak free system; the dogs breathed spontaneously.

The thoracic aorta, the pulmonary arterial wedge position, and the main pulmonary artery were catheterized from the femoral vessels under fluoroscopic control. Pulmonary wedge position was determined by catheter tip location and by pulse pres-

sure contour. Pressures were recorded at a paper speed of 10 mm per second using Statham P23Db strain gauges and the carrier amplifiers of an oscillographic recorder. Electrocardiographic Lead II was recorded simultaneously. Mean pressures were obtained by electronic damping.

Cardiac output was measured by the indicator dilution technique. Indocyanine green was injected as a sudden bolus of 2.5 mg into the pulmonary artery. Aortic blood was withdrawn through a densitometer with a constant rate withdrawal syringe. Each indicator dilution curve was replotted on semilogarithmic paper, cardiac output were calculated using the Hamilton method.¹⁶

The same protocol was used for each dog. Initial measurements of pulmonary arterial, pulmonary arterial wedge and aortic pressures were made while the dogs breathe room air approximately 15 to 20 minutes after the initiation of anesthesia. Then approximately ten minutes were permitted to elapse to ensure stability of these values before arterial P_{O_2} , P_{CO_2} , pH and cardiac output were measured. The endotracheal tube was then connected to a reservoir containing a gas mixture of 8 per cent oxygen and 92 per cent nitrogen, using a one way valve which did not permit rebreathing.

Pulmonary arterial, pulmonary wedge and aortic pressures were measured at one minute intervals after the onset of hypoxia. Measurements of heart rate, cardiac output and blood gases were repeated ten minutes after the introduction of the hypoxic stimulus. It was observed that the intrinsic variation of the mean pulmonary artery pressures was less than ± 1 mm Hg while the animals were spontaneously breathing room air. An increase of more than 1.5 mm Hg was considered a positive response to hypoxia.

Results

The results of specific measurements made are summarized in Table 1. As indicated, the two groups of dogs had comparable control arterial P_{O_2} values. Cardiac outputs and heart rates were significantly higher in the group of animals anesthetized with pentobarbital. The arterial pH was slightly but significantly lower and the P_{CO_2} values higher in the droperidol/fen-

*Sublimaze, McNeil Laboratories, Inc., Fort Washington, Pa.
†Diprival, Diamond Laboratories, Inc., Des Moines, Iowa.
‡Innovar-Vet, McNeil Laboratories, Inc., Fort Washington, Pa.

The average calculated pulmonary arterial resistance increased from 240 to 353 dynes $\text{sec}^{-1}\text{cm}^{-5}$ without significant change in the pulmonary arterial wedge pressure. This analgesic neuroleptic combination provides satisfactory anesthesia for studies of hypoxic pulmonary hypertension in dogs.

We are greatly indebted to Mr. Michael Hicklin for his valuable technical assistance and to Mrs. Linda Campbell and Mrs. Shirley Wilham for their able secretarial assistance.

REFERENCES

- 1 Motley H L, Cournand A, Werko J, Hummeltau A and Dresdale D. The influence of short periods of induced acute anoxia upon pulmonary artery pressures in man. *Am J Physiol* 150:315 1947.
- 2 Westcott, R. V., Fowler N O, Scott R C, Haverstein V D and McGuire J. Anoxia and human pulmonary vascular resistance. *J Clin. Invest* 30:957 1951.
- 3 Von Euler V S and Liljestrand G. Observations on the pulmonary arterial blood pressure in the cat. *Acta Physiol Scand* 14:301 1946.
- 4 Horner P I. Circulatory adaptations in hypoxia. *Physiol Rev* 39:687 1959.
- 5 Borst H G, Wittenberger J L, Berghurd G and McGregor M. Effects of unilateral hypoxia and hypercapnia on pulmonary blood flow distribution in the dog. *Am J Physiol* 191:446 1957.
- 6 Ayado D M, Ling J S and Schmidt C F. Effects of anoxia on pulmonary circulation reflex pulmonary vasoconstriction. *Am J Physiol* 189:253 1957.
- 7 Fishman A P. Respiratory gases in the regulation of the pulmonary circulation. *Physiol Rev* 41:214 1961.
- 8 Thilenius O G, Hoffer P B, Fitzgerald R S and Perkins J F. Response of pulmonary circulation of resting unanesthetized dogs to acute hypoxia. *Am J Physiol* 206:867 1964.
- 9 Atwell R J, Hickam J B, Pryor W W and Page E H. Reduction of blood flow through the hypoxic lung. *Am J Physiol* 166:137 1951.
- 10 Stroud R C and Rahn H. Effect of O_2 and CO_2 tensions upon the resistance of the pulmonary blood vessels. *Am J Physiol* 172:211 1953.
- 11 Giles T D and Burch G E. Anesthesia dogs and cardiovascular data. *AM HEART J* 79:141 1970.
- 12 Olmsted F and Page I H. Hemodynamic changes in dogs caused by sodium pentobarbital anesthesia. *Am J Physiol* 210:817 1966.
- 13 Yelnosky J, Katz R and Dietrich F V. A study of some of the pharmacologic actions of droperidol. *Toxicol Appl Pharmacol* 6:137 1964.
- 14 Gardocki J F and Yelnosky J. A study of some of the pharmacologic actions of fentanyl citrate. *Toxicol Appl Pharmacol* 6:48 1964.
- 15 Yelnosky J and Gardocki J F. A study of some of the pharmacologic actions of fentanyl citrate and droperidol. *Toxicol Appl Pharmacol* 6:63 1964.
- 16 Hamilton W F, Riley P L, Attyah A M, Cournand A, Howell D M, Himmelstein A, Noble R P, Remington J W, Richards D W, Wheeler N C and Witham A C. Comparison of the Fick and dye injection methods of measuring cardiac output in man. *Am J Physiol* 153:309 1948.
- 17 Fisher R. A. Statistical methods for research workers. New York 1958. Hafner Publishing Co. Inc. pp 96-97.
- 18 Ayado D M. The lung circulation. Vol I. New York 1965. Pergamon Press Ltd. pp 261-343.

The average mean pulmonary arterial pressure rose in the pentobarbital group but a higher increase of 3.5 mm Hg in the average value was found in the droperidol-fentanyl group. The "reactor" or "non-reactor" status of dogs in the pentobarbital group was not related to pH or to PCO_2 . For example, five dogs in the pentobarbital group had arterial pH values less than 7.30. Of these five, two developed a pulmonary pressor response with hypoxia and three failed to react. Six dogs in the droperidol-fentanyl group had control arterial pH values of less than 7.30; each developed a pressor response with hypoxia. Moreover, the minimal role of the arterial pH in modifying the pulmonary pressor response is indicated by the insignificant difference in arterial pH values obtained in the two groups during hypoxia. The higher heart rate and cardiac output encountered in the control state persisted after hypoxia in the pentobarbital group. That the appearance of pulmonary hypertension in the droperidol-fentanyl group reflected active pulmonary vasoconstriction is attested by the lack of change in the wedge pressure and by an increase of 73 dynes sec. cm^{-2} in the average calculated pulmonary arteriolar resistance.

The observation that the central pulmonary artery pressure was higher in dogs which received pentobarbital than in those which received droperidol-fentanyl led to chronic studies in one dog after leaving a catheter in the main pulmonary artery. The mean pulmonary arterial pressure varied from 11.5 to 12 mm Hg during anesthesia with droperidol-fentanyl. On the following day, the pressure was also 11.5 to 12 mm Hg while the dog was awake. Subsequently, administration of sodium pentobarbital (30 mg per kilogram) was associated with an increase in pulmonary arterial mean pressure to 13 and 14.5 mm Hg at five and ten minutes, respectively.

The variability in the pulmonary vascular reactivity of the pentobarbital group was further evidenced by one dog which underwent consecutive studies three days apart. A pulmonary pressor response occurred to hypoxia during the first study; no change in mean pulmonary arterial pressure occurred with exposure to the same stimulus during the second study.

Discussion

The response of the pulmonary vascular bed to hypoxia has varied widely in previous studies.⁷ The only exceptions are the report of Borst and associates,⁸ in which hypoxic pulmonary hypertension uniformly occurred in dogs after six to eight hours of anesthesia, and the report of Thilenius and associates,⁹ in intact, unanesthetized dogs. The variability reported in other studies^{3,10} seemed unlikely to reflect intrinsic differences among dogs. The influence of the anesthetic agent on the development of hypoxic pulmonary hypertension was the subject of the present study. As has been previously found, dogs studied under barbiturate anesthesia reacted variably to hypoxia. Conversely, dogs studied under droperidol-fentanyl anesthesia uniformly developed hypoxic pulmonary hypertension. This group of dogs received small amounts of atropine to counteract the sinus bradycardia produced by these agents. The effect of atropine on the pulmonary arterial pressure regardless of the change in cardiac output, is known to produce either an increase, a decrease, or no change in pressure.¹¹ One may postulate, however, that atropine could enhance the development of hypoxic pulmonary vasoconstriction by blocking the inhibitory effect of vagal stimulation on the release of histamine.¹² It has been shown that atropine does not modify the hypoxic pressor response.⁸

A combination of droperidol and fentanyl provides satisfactory anesthesia and permits the demonstration of a pulmonary vasoconstrictor response in the dogs studied. A mixture of droperidol and fentanyl may prove to be superior to pentobarbital anesthesia for physiologic experimentation in the study of hypoxic pulmonary hypertension.

Summary

Inhalation of 8 per cent oxygen produced pulmonary hypertension in only 13 of 22 dogs anesthetized with pentobarbital. Conversely, each of the dogs anesthetized with a mixture of droperidol and fentanyl developed hypoxic pulmonary hypertension ($p = 0.0055$) with an increase in the average mean pulmonary artery pressure from 9.7 ± 0.55 (S.E.) to 13.2 ± 0.77 mm Hg.

The average calculated pulmonary arterial resistance increased from 280 to 353 dynes sec cm^{-2} without significant change in the pulmonary arterial wedge pressure. This analgesic neuroleptic combination provides satisfactory anesthesia for studies of hypoxic pulmonary hypertension in dogs.

We are greatly indebted to Mr. Michael Hacklin for his valuable technical assistance and to Mrs. Linda Campbell and Mrs. Shirley Williams for their able secretarial assistance.

REFERENCES

- 1 Motley H L, Cournand A, Werko L, Himmelstein A and Dresdale D. The influence of short periods of induced acute anoxia upon pulmonary artery pressures in man. *Am. J. Physiol.* 150:315 1947.
- 2 Wescott H V, Fowler N O, Scott P C, Haverstein A D and McGuire J. Anoxia and human pulmonary vascular resistance. *J. Clin. Invest.* 30:957 1951.
- 3 Von Euler U S and Liljestrand G. Observations on the pulmonary arterial blood pressure in the cat. *Acta Physiol. Scand.* 12:301 1946.
- 4 Korner P I. Circulatory adaptations in hypoxia. *Physiol. Rev.* 39:687 1959.
- 5 Borst H G, Wittenberger J L, Berglund G and McGregor M. Effects of unilateral hypoxia and hypercapnia on pulmonary blood flow distribution in the dog. *Am. J. Physiol.* 191:145 1957.
- 6 Ayado D M, Ling J S and Schmidt C F. Effects of anoxia on pulmonary circulation reflex pulmonary vasoconstriction. *Am. J. Physiol.* 189:253 1957.
- 7 Fishman A P. Respiratory gases in the regula-

- tion of the pulmonary circulation. *Physiol. Rev.* 41:714 1961.
- 8 Thilenius O G, Hoffer P M, Fitzgerald R S and Perkins J F. Response of pulmonary circulation of resting unanesthetized dogs to acute hypoxia. *Am. J. Physiol.* 206:867 1964.
- 9 Atwell R J, Hickam J B, Pryor W W and Page E B. Reduction of blood flow through the hypoxic lung. *Am. J. Physiol.* 166:37 1951.
- 10 Stroud R C and Rahn H. Effect of O_2 and CO_2 tensions upon the resistance of the pulmonary blood vessels. *Am. J. Physiol.* 172:211 1953.
- 11 Giles T D and Burch G E. Anesthesia dogs and cardiovascular data. *AM. HEART J.* 79:141 1970.
- 12 Olmsted F and Page I H. Hemodynamic changes in dogs caused by sodium pentobarbital anesthesia. *Am. J. Physiol.* 210:817 1966.
- 13 Yelnosky J, Katz R and Dietrich E V. A study of some of the pharmacologic actions of droperidol. *Toxicol. Appl. Pharmacol.* 6:37 1964.
- 14 Gardocki J F and Yelnosky J. A study of some of the pharmacologic actions of fentanyl citrate. *Toxicol. Appl. Pharmacol.* 6:48 1964.
- 15 Yelnosky J and Gardocki J F. A study of some of the pharmacologic actions of fentanyl citrate and droperidol. *Toxicol. Appl. Pharmacol.* 8:63 1964.
- 16 Hamilton W F, Riley H L, Attyah A M, Cournand A, Fowell D M, Himmelstein A, Noble R P, Remington J W, Richards D W, Wheeler N C and Witham A C. Comparison of the Fick and dye injection methods of measuring cardiac output in man. *Am. J. Physiol.* 153:309 1948.
- 17 Fisher R. A. Statistical methods for research workers. New York 1958. Hafner Publishing Co. Inc. pp. 96-97.
- 18 Ayado D M. The lung circulation. Vol. 1. New York 1965. Pergamon Press Ltd. pp. 261-343.

The average mean pulmonary arterial pressure rose in the pentobarbital group but a higher increase of 3.5 mm Hg in the average value was found in the droperidol fentanyl group. The 'reactor' or 'non reactor' status of dogs in the pentobarbital group was not related to pHi or to PCO_2 . For example five dogs in the pentobarbital group had arterial pHi values less than 7.30. Of these five, two developed a pulmonary pressor response with hypoxia and three failed to react. Six dogs in the droperidol fentanyl group had control arterial pHi values of less than 7.30, each developed a pressor response with hypoxia. Moreover, the minimal role of the arterial pHi in modifying the pulmonary pressor response is indicated by the insignificant difference in arterial pHi values obtained in the two groups during hypoxia. The higher heart rate and cardiac output encountered in the control state persisted after hypoxia in the pentobarbital group. That the appearance of pulmonary hypertension in the droperidol fentanyl group reflected active pulmonary vasoconstriction is attested by the lack of change in the wedge pressure and by an increase of 73 dynes sec cm^{-2} in the average calculated pulmonary arteriolar resistance.

The observation that the central pulmonary artery pressure was higher in dogs which received pentobarbital than in those which received droperidol fentanyl led to chronic studies in one dog, after leaving a catheter in the main pulmonary artery. The mean pulmonary arterial pressure varied from 11.5 to 12 mm Hg during anesthesia with droperidol fentanyl. On the following day, the pressure was also 11.5 to 12 mm Hg while the dog was awake. Subsequently administration of sodium pentobarbital (30 mg per kilogram) was associated with an increase in pulmonary arterial mean pressure to 13 and 14.5 mm Hg at five and ten minutes, respectively.

The variability in the pulmonary vascular reactivity of the pentobarbital group was further evidenced by one dog which underwent consecutive studies three days apart. A pulmonary pressor response occurred to hypoxia during the first study, no change in mean pulmonary arterial pressure occurred with exposure to the same stimulus during the second study.

Discussion

The response of the pulmonary vascular bed to hypoxia has varied widely in previous studies.⁷ The only exceptions are the report of Borst and associates⁴ in which hypoxic pulmonary hypertension uniformly occurred in dogs after six to eight hours of anesthesia, and the report of Thilenius and associates,⁸ in intact, unanesthetized dogs. The variability reported in other studies¹ seemed unlikely to reflect intrinsic differences among dogs. The influence of the anesthetic agent on the development of hypoxic pulmonary hypertension was the subject of the present study. As has been previously found dogs studied under biturate anesthesia reacted variably to hypoxia. Conversely, dogs studied under droperidol fentanyl anesthesia uniformly developed hypoxic pulmonary hypertension. This group of dogs received small amounts of atropine to counteract the sinus bradycardia produced by these agents. The effect of atropine on the pulmonary arterial pressure, regardless of the change in cardiac output, is known to produce either an increase or decrease, or no change in pressure.¹² One may postulate, however, that atropine could enhance the development of hypoxic pulmonary vasoconstriction by blocking the inhibitory effect of vagal stimulation on the release of histamine.¹³ It has been shown that atropine does not modify the hypoxic pressor response.⁷

A combination of droperidol and fentanyl provides satisfactory anesthesia and permits the demonstration of a pulmonary vasoconstrictor response in the dogs studied. A mixture of droperidol and fentanyl may prove to be superior to pentobarbital anesthesia for physiologic experimentation in the study of hypoxic pulmonary hypertension.

Summary

Inhalation of 8 per cent oxygen produced pulmonary hypertension in only 1 of 22 dogs anesthetized with pentobarbital. Conversely, each of the dogs anesthetized with a mixture of droperidol and fentanyl developed hypoxic pulmonary hypertension ($p = 0.0055$) with an increase in the average mean pulmonary artery pressure from 9.7 ± 0.55 (SE) to 13.2 ± 0.77 mm Hg.

Table 1 Hemodynamic results of coronary embolization and effects of dopamine (mean \pm SE M)

Parameters	Control (N = 1)	Postembolic (N = 1)	Dopamine		No drugs (N = 10)
			20 min (N = 1)	60 min (N = 1)	
Heart rate (beats/min)	150 \pm 7 ^a	157 \pm 5.4	151 \pm 6.9	151 \pm	148 \pm 4.5
Cardiac output (L/min)	4.19 \pm 0.40	0.3 \pm 0.17	6 \pm 0.21	3.4 \pm 0.14	1.5 \pm 0.14
LV stroke volume (ml/beat)	6.1 \pm 0.9	13.3 \pm 1.0	1.4 \pm 1.3	15 \pm 1.7	1 \pm 1.00
LV systolic pressure (mm. Hg)	173 \pm 10	140 \pm 11.0	157 \pm 11.6†	149 \pm 11.0	144 \pm 9.5
LV end-diastolic pressure (mm. Hg)	7.3 \pm 1.0	1.8 \pm .4	14 \pm .6†	14.8 \pm 0.4	19.5 \pm 3.3
Mean aortic pressure (mm. Hg)	14 \pm 8.0	128 \pm 9.6	134 \pm 9.8	130 \pm 10.1	11 \pm 9.0
Systemic vascular resistance (dynes sec. cm. ⁻⁵)	990 \pm 308	5256 \pm 351	4340 \pm 470†	400 \pm 478	4090 \pm 411†
LV minute work (Kg. M/min)	9.3 \pm 1.3	3.5 \pm 0.5	5.1 \pm 0	4.4 \pm 0.6	0.8 \pm 0.4
LV stroke work (Gm M/min)	58.0 \pm 7.4	3 \pm 3.3	33.8 \pm 4.5	0.8 \pm 4.3	19.4 \pm 3.0
LV peak dP/dt (mm. Hg/sec)	3060 \pm 337	0.17 \pm 0.00*	35.6 \pm 419	33.8 \pm 335	1.930 \pm 104
Pressure-time index (mm. Hg. beat/min. 10 ⁻³)	201 \pm 18	0.1 \pm 18	0.25 \pm 19	0.01 \pm 16	191 \pm 13

N = No. of d.s.

*p < 0.01

†p < 0.05

D. all. r. f. s. i. s. f. c. e. f. p. u. e. d. f. e. r. e. n. c. e. s.

with the electrocardiogram using a multi-channel photographic recorder (Electronics for Medicine). The first derivative of the left ventricular pressure (LV dP/dt) was obtained by electronic differentiation. Cardiac output was measured by the indicator dilution technique: indocyanine green (2.5 mg) being injected into the main pulmonary artery and sampled continuously from the descending aorta through a Waters NP 302 densitometer using a Gilford constant flow infusion withdrawal pump and the curves calibrated by the Spahr method.⁸ Systemic and pulmonary vascular resistances and left ventricular stroke and minute work were calculated by standard formulas. A pressure-time index was obtained as the product of the left ventricular systolic pressure and heart rate.⁹ Selective embolization of the left coronary artery was performed using a modification of the technique of Ilch and associates¹⁰ as

described previously.^{11,12} Postembolic control measurements were obtained 90 to 120 minutes after the second mercury injection at which time a stable hemodynamic state and heart rhythm were present.

Dopamine* was infused at the rate of 5 μ g per kilogram per minute into a peripheral vein and the hemodynamic responses determined at 20 and 60 minutes. Where dopamine caused persistent ventricular dysrhythmias the infusion was reduced to 2.2 μ g per kilogram per minute. Final hemodynamic measurements were made 30 minutes after stopping the dopamine infusion.

Results

The hemodynamic changes produced by coronary embolization, dopamine infusion and final control values are given in Table I.

*Obtained from the gift of Dr. A. N. Stone, Laboratory, Alou, P. M. I.

The effects of dopamine on depressed myocardial function following coronary embolization in the closed-chest dog

Harry Ipp, M.D., M.B.S., M.A., I.C.P.

Raul E. Talicov, M.D.

Leon Resnick, M.D., I.A.C.P.

Sheila King

Chicago, Ill.

Sympathomimetic amines increase myocardial contractility and are used to treat cardiogenic shock and severe cardiac failure.^{1,2} While norepinephrine, epinephrine, and isoproterenol have been the most frequently administered drugs for their positive inotropic effect, excess alpha or beta adrenergic receptor stimulation has frequently limited their ultimate effectiveness.^{3,4} Dopamine (3,4-dihydroxyphenyl ethylamine) an immediate metabolic precursor of norepinephrine has been suggested as an alternative drug and preliminary studies have been published documenting its effect in the management of cardiogenic shock and severe cardiac failure.^{5,7}

This study reports the hemodynamic effects of dopamine on depressed myocardial function produced in the closed chest dog by mercury embolization of the left coronary arterial system.

Method

Twelve mongrel dogs whose weights varied from 25 to 34 kilograms were anes-

thetized with sodium pentobarbital (75 mg per kilogram). Additional muscle relaxation was induced with intermittent 70 mg doses of succinylcholine as needed. Respiration was maintained by room air delivered through a cuffed endotracheal tube from a positive pressure pump (Harvard). Arterial P_{O_2} , P_{CO_2} , and pH were monitored frequently throughout the experiment and adjustments made to the respiratory cycle as needed. Metabolic acidosis was corrected by intermittent intravenous injections of 20 to 40 mEq of sodium bicarbonate as required. Dacron catheters (7 or 8 Fr) were placed in the ascending aorta and main pulmonary artery from the left femoral artery and vein respectively under fluoroscopic control. High fidelity left ventricular pressure recordings were obtained by transthoracic insertion of a 4 inch semirigid Teflon catheter (Becton Dickinson & Co) attached directly to the pressure transducer. All pressures were measured with reference to the midchest position using Statham P23Db transducers and recorded simultaneously

From the Department of Medicine, Section of Cardiology, University of Chicago, Pritzker School of Medicine, Chicago, Ill.

Supported in part by United States Public Health Service Contract 43-57-1331, Medical Staff, Research Triangle Corporation, 057-03-05, a United Chicago Heart Association.

Received for publication Oct 4, 1971.

Reprint requests to: L. Resnick, M.D., University of Chicago, 950 S. 59th St., Box 124, Chicago, Ill. 60637.

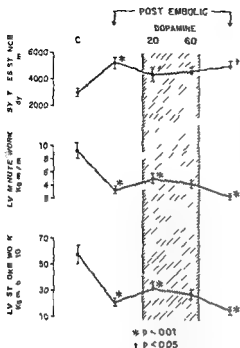


Fig 1C Hemodynamic result (LV stroke work, LV minute work, systemic resistance) of coronary embolization and the effects of dopamine infusion at 0 minutes and 60 minutes after the postembolization on control determinations

Discussion

Despite the vigorous administration of a variety of sympathomimetic amines the mortality rate from cardiogenic shock remains unacceptably high.⁴ These pharmacologic agents act through varying degrees of beta- and alpha-adrenergic stimulation.¹² Excessive alpha-adrenergic stimulation may impair peripheral and visceral perfusion¹³ and increase myocardial afterload thereby reducing cardiac output and increasing myocardial oxygen consumption.^{14,15} Excessive beta-adrenergic stimulation despite its significant inotropic effect may produce a fall in systemic blood pressure and hence in coronary artery perfusion.¹⁶ The associated sinus tachycardia further increases myocardial oxygen consumption and ventricular rhythm disturbances may emerge.¹⁷ Of even greater concern are reports of subendocardial necrosis following large doses of sympathomimetic amines¹⁸ and more recently extension of ischemic zones surrounding the infarct as defined

by electrocardiographic surface mapping techniques have been noted.¹⁹

Dopamine (3,4-dihydroxyphenylethylamine), a naturally occurring catecholamine and immediate precursor of norepinephrine produces both alpha- and beta-adrenergic stimulation.^{20,21} Hemodynamic studies in normotensive human subjects and animals have demonstrated increased cardiac output and myocardial contractility mediated through beta-adrenergic stimulation. The peripheral vascular response has been variable depending on the species of animal and the dose administered.⁷ In the normal human subject increased myocardial contractility is associated with a fall in systemic vascular resistance and minimal change in heart rate and arterial blood pressure.²²

Dopamine induces vasodilation of the renal^{23,24} and mesenteric vascular beds.²⁵ Improvement in renal plasma flow, glomerular filtration and sodium clearance have been documented. This property is not related to beta-adrenergic stimulation and appears unique to dopamine. In contrast commonly used agonist agents may reduce renal blood flow through renal artery constriction by reduction in perfusing pressure or shunting blood from the kidneys to the extremities.⁶

Studies using dopamine in the intact animal preparation with depressed myocardial function have been few. Wintroub and associates⁸ induced myocardial depression by ligation of the anterior descending coronary artery in the open chest dog. Significant increases in cardiac output, LV dP/dt associated with fall in systemic vascular resistance occurred. Heart rate and mean arterial blood pressure remained unchanged. Carvalho and associates²⁷ utilizing either circumflex coronary artery ligation or microsphere embolization in an open chest preparation noted similar results. Systemic vascular resistance however remained unchanged and both the heart rate and mean blood pressure rose. Significant increase in coronary blood flow occurred. In both these studies myocardial irritability during dopamine infusion was not a significant problem.

In the present study mercury embolization of the left coronary artery of the dog

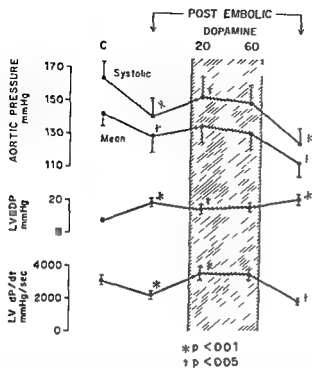


Fig 1A Hemodynamic results (LV dP/dt, LVEDP, and aortic pressure) of coronary embolization and the effects of dopamine infusion at 20 minutes and 60 minutes after the postembolization control determinations

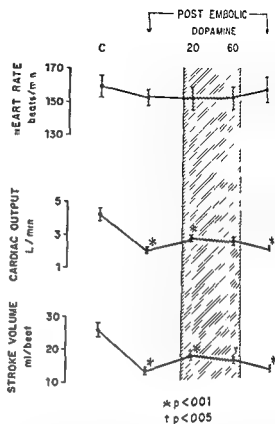


Fig 1B Hemodynamic results (stroke volume, cardiac output, and heart rate) of coronary embolization and the effects of dopamine infusion at 20 minutes and 60 minutes after the postembolization control determinations

and shown graphically in Fig 1. All results were analyzed statistically and represent the mean \pm S.E.M. of the 12 experiments.

Selective embolization of the left coronary arterial system. Ninety to 120 minutes following selective embolization of the left coronary artery the cardiac output fell by 52 per cent, stroke volume by 49 per cent, left ventricular peak dP/dt by 29 per cent, left ventricular systolic pressure by 14 per cent, left ventricular stroke work by 60 per cent, and pressure time index by 18 per cent. In contrast, the systemic vascular resistance increased 77 per cent and left ventricular end diastolic pressure from a control value of 7 to a value of 18 mm Hg.

Dopamine infusion. Twenty minutes after starting the dopamine infusion significant increases in cardiac output (30 per cent), stroke volume (31 per cent), stroke work (46 per cent), left ventricular dP/dt (64 per cent), and left ventricular systolic pressure (8 per cent) were recorded. The systemic vascular resistance decreased by 18 per cent and the left ventricular end diastolic pressure decreased from 18 to 14 mm Hg. Heart rate and mean aortic

pressure did not change significantly.

After 60 minutes of continuous dopamine infusion a significant decrease in stroke volume occurred (14 per cent) with all other parameters remaining unchanged.

Cessation of dopamine. Thirty minutes after stopping the dopamine infusion marked hemodynamic deterioration occurred with significant reduction in cardiac output (21 per cent), stroke volume (23 per cent), stroke work (38 per cent), peak LV dP/dt (45 per cent), and pressure time index (13 per cent). The systemic vascular resistance increased (9 per cent) and the left ventricular end-diastolic pressure rose from 15 to 20 mm Hg; the heart rate remained unchanged.

Persistent ventricular dysrhythmias occurred in 6 dogs and in 4 recurrent ventricular tachycardia necessitated reducing the dopamine infusion from 5 to 2.2 μ g per kilogram per minute. Ventricular fibrillation did not occur during the infusion of the drug.

persistent ventricular tachycardia. It is concluded that dopamine will improve depressed myocardial function following acute coronary arterial embolization at least temporarily but that the incidence of various ventricular dysrhythmias may well limit its use.

REFERENCES

- 1 MacLennell H L and Moran N C Pharmacological basis for the use of adrenergic agonists and antagonists in cardiovascular shock and hypotension *Progr Cardiovasc Dis* 10:55 1967
- 2 Goldberg L J Use of sympathomimetic amines in heart failure *Am J Cardiol* 23:177 1968
- 3 Gunnar P M, Loeb H S and Tobin J R Jr Ineffectiveness of isoproterenol in shock due to acute myocardial infarction *JAMA* 209:1224 1961
- 4 Kuhn L A Shock in myocardial infarction—medical treatment *Am J Cardiol* 26:518 1970
- 5 MacLennell H L, McNay J L, Meyer M B and Goldberg L J Dopamine in the treatment of hypotension and shock *N Engl J Med* 275:1389 1966
- 6 McDonald M H Jr, Goldberg L I, McNay J L and Tuttle E P Effects of dopamine in man: augmentation of sodium excretion, glomerular filtration rate and renal plasma flow *J Clin Invest* 43:1116 1964
- 7 Goldberg L I, Talley R C and McNay J L The potent role of dopamine in the treatment of shock *Progr Cardiovasc Dis* 19:40 1969
- 8 Spirling C M, Mook C A, Nieren J, van der Walke L B and Zijlstra W G Calibration of dye dilution curves for calculating cardiac output and central blood volume in the Tetra European de Corda bei nt a Conventus Rome 1960 *Excerpta Medica* p 595
- 9 McDonald R H Jr, Taylor R H and Chinolan H E Measurement of myocardial developed tension and its relation to oxygen consumption *Am J Physiol* 211:667 1966
- 10 Jlich S, Mogulovsky H C, Pietra G, Shaffer D B, Birch S J and Fihman A P A reproducible model of cardiac shock in the dog *Circulation* 39:705 1969
- 11 Falcoy R F, Resnekov L and Jung S The effects of coupled and paired ventricular stimulation following acute myocardial infarction in dogs *Am Heart J* 82:571 1971
- 12 Moran N C Evaluation of the pharmacologic basis for therapy of circulatory shock *Am J Cardiol* 26:571 1970
- 13 Nickerson M A, Second edition and revised edition Herhey S C editor *Shock* Boston 1964 Little Brown & Company p 227
- 14 Haddy J J Pathophysiology and therapy of the shock of myocardial infarction *Ann Intern Med* 79:809 1970
- 15 Swan H J C, Forrester J S, Danzow J and Allen H A Power failure in acute myocardial infarction *Progr Cardiovasc Dis* 12:568 1970
- 16 Danell H B, Bagwell F E and Walton L P Limitation of myocardial function by reduced coronary blood flow during isoproterenol action *Circ Res* 21:85 1967
- 17 Kuhn L A, Kline H J, Goodman J, Johnson C D and Marino A J Effects of isoproterenol on hemodynamic alterations myocardial metabolism and coronary flow in experimental acute myocardial infarction with shock *Am Heart J* 71:777 1969
- 18 Ferrans V J, Hubs R G, Black W C and Weibrecht D G Isoproterenol induced myocardial necrosis: A histological and electron microscopic study *Am Heart J* 68:171 1964
- 19 Maroko P R, Kjekhus J K, Sobel B E, Watanabe T, Covell J W, Ross J Jr and Braunwald E Factors influencing infarct size following experimental coronary artery occlusions *Circulation* 43:67 1971
- 20 Black W L and Rolett E L Dopamine induced alterations in left ventricular performance *Circ Res* 19:71 1966
- 21 Black W L and Rolett E L Cardiovascular adrenergic activity of dopamine in the dog *Am Heart J* 70:333 1968
- 22 Horowitz D, Fox S M and Goldberg L I Effects of dopamine in man *Circ Res* 10:337 1967
- 23 McNay J L and Goldberg L I Comparison of the effects of dopamine, isoproterenol, norepinephrine and bradycinin on canine renal and femoral blood flow *J Pharmacol Exp Ther* 151:73 1966
- 24 Meyer M H, McNay J L and Goldberg L I Effects of dopamine on renal function and hemodynamics in the dog *J Pharmacol Exp Ther* 156:186 1967
- 25 Fible J N A proposed mechanism for the depressant effect of dopamine in the anesthetized dog *J Pharmacol Exp Ther* 145:64 1964
- 26 Wintroub M A, Schroeder J S, Schroll M, Robinson S I and Harrison D C Hemodynamic response to dopamine in experimental myocardial infarction *Am J Physiol* 217:1716 1969
- 27 Carvalho M, Wyden J K, Bernstein H, Gold H and Corday E Hemodynamic effects of 3-hydroxytryptamine (dopamine) in experimentally induced shock *Am J Cardiol* 23:717 1969
- 28 Karlner J S and Ross J Jr Left ventricular performance after acute myocardial infarction *Progr Cardiovasc Dis* 13:374 1971
- 29 Brooks H I, Stein P D, Matson J I and Hyland J W Dopamine induced alterations in coronary hemodynamics in dogs *Circ Res* 24:199 1969
- 30 Goldberg L I, MacLennell H L, McNay J L and Meyer M B The use of dopamine in the treatment of hypotension and shock

provided a reproducible model of depressed myocardial function in the intact animal resembling that seen in patients with extensive myocardial infarction²³. This hemodynamic response is characterized by a fall in cardiac output and work, mean blood pressure, and left ventricular dP/dt, and by a rise in left ventricular end diastolic pressure and systemic vascular resistance.¹¹

Dopamine significantly improved myocardial function as shown by an increase in cardiac output, stroke volume, left ventricular dP/dt, and left ventricular stroke work and by a fall in left ventricular end diastolic pressure. A positive inotropic response to dopamine was indicated by the increase in left ventricular dP/dt associated with an unchanged heart rate, mean blood pressure and a fall in systemic vascular resistance and left ventricular end diastolic pressure.

Although coronary blood flow was not determined in the present study, dopamine is a potent stimulator of coronary blood flow. The induced coronary vasodilation is however secondary to increased myocardial oxygen demands.²⁹

The evaluation of dopamine in the treatment of cardiac failure^{2,6} and cardiogenic shock^{4,7} in patients has been limited. Significant diuretic response characterized by increased glomerular filtration rate and sodium excretion was noted in patients with congestive cardiac failure. Marked hemodynamic improvement occurred in 3 of 7 patients with cardiogenic shock following acute myocardial infarction or cardiac surgery. These patients had been refractory to norepinephrine, epinephrine and mannitol.³⁰ In shock due to varying etiologies comparative hemodynamic studies of dopamine and the other commonly used sympathomimetic amines suggested dopamine to be more effective than isoproterenol in the presence of normal or reduced peripheral vascular resistance³¹ and superior to norepinephrine in patients requiring little elevation in mean arterial pressure.³ Unlike norepinephrine and isoproterenol which produced transmyocardial lactate Winslow and associates³² observed increased myocardial lactate extraction in shocked patients treated with dopamine.

Of particular concern in this study was the high incidence of ventricular dysrhythmias unassociated with significant chronotropic response. Rhythmic disturbances have not been documented as a significant problem even when dopamine was used in higher doses than in the current study. While the increased myocardial irritability might be a reflection of the model of depressed myocardial function used, significant dysrhythmias were not observed in a similar animal preparation infused with low-dose isoproterenol and aminophylline.³⁴

This study demonstrates that dopamine significantly improves myocardial function when acutely depressed. The pharmacologic properties of the amine appear advantageous, for not only is there improvement in cardiac function but also renal function. The emergence of ventricular dysrhythmias however is of concern and requires further evaluation.

Summary

Severe myocardial depression was induced in 12 anesthetized closed chest dogs by mercury embolization of the left coronary artery and the effects of dopamine infusion (5 µg per kilogram per minute) studied. Coronary embolization produced decreases in cardiac output (CO) of 52 per cent, stroke volume (SV) of 49 per cent, left ventricular peak dP/dt (LVdP/dt) of 29 per cent, stroke work (SW) of 60 per cent, LV systolic pressure (LVSP) of 14 per cent and an increase in systemic vascular resistance (SVR) of 77 per cent. LV end diastolic pressure (LVEDP) increased from 7 to 18 mm Hg. After 70 minutes of dopamine, CO increased 30 per cent, SV 31 per cent, SW 46 per cent, LVdP/dt 64 per cent and LVSP 8 per cent, SVR decreased 18 per cent and LVEDP was 14 mm Hg (all changes $p < 0.05$). Heart rate and mean aortic pressure did not change. After 60 minutes of dopamine, slight deterioration occurred but most parameters were still significantly improved. Thirty minutes after stopping dopamine, marked circulatory deterioration recurred. Persistent ventricular dysrhythmias occurred in 6 dogs, in 4 of whom dopamine dosage had to be decreased to 2.5 µg per kilogram per minute because of

Effect of caffeine on the ventricular fibrillation threshold in normal dogs and dogs with acute myocardial infarction

Samuel Bellet MD*

Eckhard Horstmann MD**

Laurian R. Roman MD***

Norberto T. DeGuzman MD****

John B. Kostis MD*****

Philadelphia Pa

Recently our laboratory as well as others has been interested in studying the various stress effects of caffeine such as the elevation of plasma adrenocortical steroid concentrations, blood free fatty acid levels and adrenergic effects.¹⁻⁹ In addition, caffeine may increase the concentration of cyclic adenosine monophosphate (AMP) by competitive inhibition of phosphodiesterase and may decrease the binding of Ca⁺⁺ by the cell membrane.⁹⁻¹⁰ Because some of these pharmacologic effects are known to induce ventricular fibrillation,¹¹⁻¹² it would be of interest to study the effect of caffeine on the ventricular fibrillation threshold (VFT).

The aim of the present work was to study the effect of caffeine on the VFT in normal dogs and in dogs with experimentally

induced myocardial infarction during the acute stage of the occlusion. In order to evaluate the relation of the changes in VFT after the administration of caffeine to the adrenergic effects, experiments were also performed after pretreatment with propranolol and with practolol.

Methods and materials

Mongrel dogs weighing 25 to 30 pounds were anesthetized intravenously with sodium pentobarbital 25 mg per kilogram of body weight. Respiration with room air was maintained by means of a Harvard ventilatory pump through an endotracheal tube. Tidal volume and respiratory rate were set according to the weight of the animal utilizing the ventilatory graph prepared by Kleinman and Radford. Arterial

*Fellow in the Division of Cardiology, Philadelphia General Hospital, Philadelphia, Pa.

**Fellow in the Division of Cardiology, Philadelphia General Hospital, Philadelphia, Pa.

Received for publication Oct. 15, 1971.

Reprint requests to Samuel B. Bellet, MD, 2021 Spruce St., Philadelphia, Pa. 19103.

Director, Division of Cardiology, Philadelphia General Hospital, Professor of Clinical Cardiology, Graduate School of Medicine of the University of Pennsylvania, Philadelphia, Pa.

***Cardiology Chief Resident, Division of Cardiology, Philadelphia General Hospital.

****Fellow, Division of Cardiology, Philadelphia General Hospital.

*****Research Associate, Division of Cardiology, Philadelphia General Hospital.

- after myocardial infarction or cardiac surgery
Am Heart J 72:568, 1966
- 31 Tilley R C, Goldberg L I, Johnson C E
and McNay J L Hemodynamic comparison
of dopamine and isoproterenol in patients with
shock *Circulation* 39:361, 1969
- 32 Gunnar R, Loeb H, Pietra R, Ortiz J
and Tobin J, Jr Hemodynamic effects of
dopamine compared to norepinephrine and
isoproterenol in clinical shock *Circulation*
38 (Suppl VI):91, 1968
- 33 Winslow E, Loeb H, Rahimtoola S,
Rosen K, Gunnar R Transmyocardial
metabolism during treatment of shock
catecholamines *Circulation* 42 (Suppl III)
1970
- 34 Filicev R E, Lipp H, Resnekov L,
King S The effects of low dose isoproter-
enol and aminophylline following acute myoca-
rdial infarction in dogs *Cardiovasc Res* Subm
for publication

Table 1 Effect of sodium benzoate on the ventricular fibrillation threshold in intact normal dogs*

Dog	Minutes after intravenous injection					
	0	15	30	45	60	90
1	0.50†	0.50	0.45	0.50	0.55	0.50
2	0.45	0.45	0.50	0.45	0.45	0.45
3	0.45	0.40	0.40	0.40	0.40	0.40
4	0.35	0.35	0.40	0.35	0.40	0.35
5	0.40	0.70	0.70	0.40	0.40	0.70
6	0.50	0.50	0.45	0.50	0.50	0.50
7	0.40	0.70	0.70	0.75	0.75	0.75
8	0.60	0.60	0.60	0.60	0.45	0.45
9	0.30	0.30	0.30	0.70	0.70	0.75
10	0.45	0.40	0.45	0.45	0.55	0.55

Time after drug admin (min)	No. of dogs	Mean VFT (watt sec)	Mean difference from 0 time value (watt sec)	Variance	SE M	t	P
0	10	0.50					
15	10	0.49	0.01	0.0444	0.067	0.149	NS†
30	10	0.495	0.005	0.00136	0.011	0.454	NS
45	10	0.49	0.01	0.00155	0.012	0.833	NS
60	10	0.495	0.005	0.0058	0.04	0.08	NS
90	10	0.49	0.01	0.0043	0.02	0.50	NS

Dose: 12.5 mg/kg body weight
VFT: watt sec

Differences statistically significant at the 5% level by paired comparison.

wall and were thus available for stimulation

Group A In the first group (Group A intact dogs) a method similar to that described by Lown, Kleiger and Williams¹² was utilized. Caffeine and control experiments were performed on normal dogs and on dogs with acute myocardial infarction. The method is briefly as follows. Two electrode paddles measuring 8½ cm in diameter covered with conductive paste were applied with pressure externally on both sides of the shaved chest at the level of the apical thrust. These paddles were held in a fixed position with rubber straps across the chest. Electrical discharges were delivered utilizing the Town Cardioverter Model 105301 with a 16 microfarad capacitor through a 100 millihenry inductor. A voltage-dividing network was connected in series with the electrodes in order to obtain

accurate measurement of the discharge at the range of 0 to 10 wsec (watt seconds) at increments of 0.05 wsec. The fibrillation threshold was determined by sweeping the Q-T interval of the cardiac cycle with stimuli of increasing energy from subthreshold to threshold levels. This was performed by progressively increasing the delay of the stimulus from the peak of the H wave by increments of 10 milliseconds using a 15 to 20 second interstimulus interval. The criterion of the VFT was the minimal energy producing ventricular fibrillation for at least 10 seconds. The presence of ventricular fibrillation was established by the FCC and the disappearance of pulsatile aortic pressure (Fig. 1). Countershocks with energy ranging from 50 to 200 wsec were applied in order to convert ventricular fibrillation to normal sinus rhythm. After an episode of ventricular

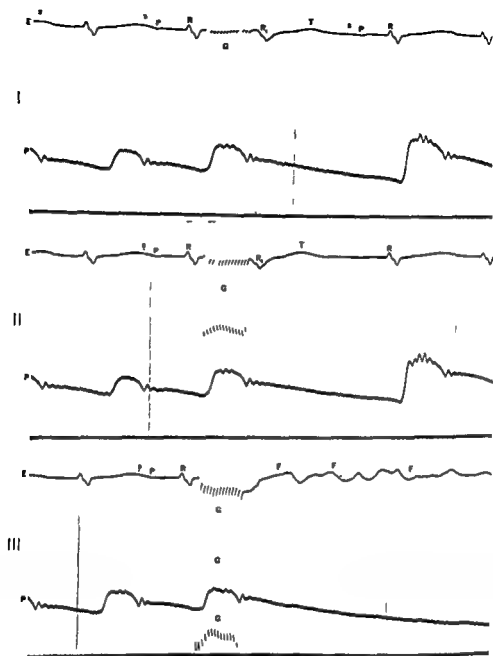


FIG. 1. Determination of the ventricular fibrillation threshold (VFT) by delivering a gated series of impulses (G) through previously implanted epicardial electrodes. S piezoelectric stimulus; R ventricular complex; F ventricular fibrillation. Note the progressive increase of the amplitude of the gated impulse (G) from I to III.

pH, P_{CO_2} and PO_2 were monitored by the use of a radiometer. The values did not show significant deviation from the normal. The temperature was recorded every 15 minutes by means of a rectal thermometer. The electrocardiogram (ECG) was monitored through an oscilloscope and recorded each time the VFT was measured with a Sanborn Viso 100 recorder at a paper speed of 50 mm per second. The blood pressure was measured by means of a catheter inserted in the descending aorta

utilizing Statham 23Bd transducers and Electronics for Medicine amplifiers.

Two groups of experiments were performed. In the first group the ventricular fibrillation threshold (VFT) was determined in intact dogs by delivering electrical impulses through the chest wall. In the second group the impulses were delivered directly to the heart through previously implanted epicardial electrodes. These electrodes were attached to insulated wires which were exteriorized through the chest

Table III Effect of sodium benzoate on the ventricular fibrillation threshold in normal dogs with bipolar implanted electrodes (third to seventh day after implantation)*

Dog	Minutes after intravenous injection						
	0	15	30	45	60	90	120
1	14†	16	14	16	16	16	15
2	16	15	13	16	15	15	13
3	18	17	18	18	19	19	16
4	16	18	18	16	15	18	—
5	12	11	11	13	13	11	12
6	10	9	10	10	9	10	10
7	9	11	10	10	10	11	9
8	17	19	20	18	19	19	18
9	12	11	11	11	17	12	10
10	12	12	17	13	9	12	14

Time after admin of sodium benzoate (min)	No of dogs	Mean VFT (Ma)	Mean difference from 0 time value (Ma)	Variance	SE M	t	P
0		13.6					
15	10	13.9	0.3	2.233	0.47	0.64	NS†
30	10	13.7	0.1				NS
45	10	14.1	+0.5	0.7272	0.269	1.859	NS
60	10	13.7	0.1				NS
90	10	14.3	+0.7	1.555	0.394	1.776	NS
120	10	13.0	-0.3	2.4444	0.494	0.668	NS

*Dose: 12.5 mg per 100 gram of body weight

†VFT in millivolts.

‡Diff. is not statistically significant

planted electrodes) electrical discharges were delivered directly to the myocardium by means of specifically constructed bipolar epicardial electrodes implanted on the right ventricle three to seven days prior to the experiment. These electrodes consist of two stainless steel wires 1 mm in diameter embedded 10 mm apart in a small acrylic plaque. They were connected to Teflon coated treated silver wires which were extensorized through the chest wall. The heart rate was kept constant during each experiment by pacing the right atrium at a rate above the spontaneous rate of the animal by means of a similar pair of implanted electrodes. An American Electronic Laboratory stimulator was utilized for this purpose. The pacemaker impulse was double the pacing threshold in intensity and

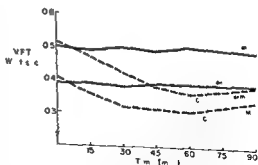


Fig. 2 The effect of caffeine on the VFT of normal dogs and dogs with acute myocardial infarction (impulses delivered through the chest wall). No change in the normal control following caffeine administration on the VFT drops. The control values of dogs with acute myocardial infarction (A M) are lower than normal. Further decreases observed after caffeine.

Table II Effect of caffeine sodium benzoate on ventricular fibrillation threshold in intact normal dogs*

Dog	Minutes after intravenous injection					
	0	15	30	45	60	90
1	0.65†	0.50	0.55	0.50	0.55	0.40
2	0.50	0.50	0.35	0.30	0.30	0.35
3	0.50	0.50	0.40	0.40	0.45	0.45
4	0.50	0.40	0.35	0.35	0.35	0.35
5	0.40	0.40	0.35	0.30	0.35	0.35
6	0.50	0.45	0.40	0.35	0.25	0.35
7	0.45	0.45	0.50	0.40	0.35	0.35
8	0.50	0.45	0.35	0.30	0.30	0.40
9	0.55	0.55	0.50	0.40	0.30	0.40
10	0.35	0.30	0.30	0.30	0.25	0.25
11	0.70	0.70	0.60	0.60	0.50	0.55

Time after admin. of caffeine (min)	No. of dogs	Mean VFT (watt sec)	Mean difference from 0 time value (watt sec)	Variance	SE V	t	P
0	11	0.509					
15	11	0.473	0.036	0.007546	0.0152	3.368	0.05
30	11	0.423	0.086	0.001307	0.0110	7.818	0.001
45	11	0.382	0.127	0.002682	0.0120	10.380	0.001
60	11	0.359	0.150	0.005500	0.0224	6.696	0.001
90	11	0.382	0.127	0.003182	0.0170	7.470	0.001

*Dosage 25 mg per kilogram of body weight.
†VFT in watt seconds.

fibrillation a period of at least 10 minutes was allowed before a new series of stimuli were applied.

The ventricular fibrillation threshold (VFT) was determined in 11 normal dogs at 15 minute intervals before and for a period of 90 minutes after intravenous injection of 25 mg per kilogram of body weight caffeine sodium benzoate (corresponding to 12.5 mg per kilogram of body weight caffeine base). Control experiments of the same duration in which sodium benzoate (12.5 mg per kilogram of body weight) was injected, were performed in 11 other dogs.

Similar studies were performed also in dogs during the acute phase of myocardial infarction produced by two stage ligation of the anterior descending artery.¹² The

experiments were performed on the fourth day after coronary ligation because in an earlier stage the presence of frequent premature ventricular contractions interferes with the proper determination of the VFT. Caffeine experiments were performed in 11 dogs with acute infarction, whereas control experiments were performed in 6 such dogs.

In addition similar experiments were performed on 9 normal animals treated by a combination of caffeine sodium benzoate (25 mg per kilogram of body weight) and propranolol (0.2 mg per kilogram of body weight). Five other animals were treated with intravenous injections of propranolol (0.2 mg per kilogram of body weight) alone.

Group B. In the second group of experiments (Group B dogs with previously im-

Table V Effect of sodium benzoate on the ventricular fibrillation threshold in dogs with acute myocardial infarction (fourth postoperative day)*

Dog	Minutes after intravenous injection					
	0	15	30	45	60	90
1	0.30†	0.45	0.45	0.45	0.45	0.50
2	0.30	0.55	0.55	0.55	0.55	0.50
3	0.15	0.45	0.50	0.40	0.45	0.45
4	0.40	0.15	0.45	0.45	0.40	0.3
5	0.35	0.35	0.35	0.45	0.30	0.30
6	0.20	0.20	0.20	0.20	0.20	0.20
7	0.50	0.30	0.30	0.30	0.30	0.30
8	0.50	0.45	0.45	0.45	0.45	0.50
9	0.45	0.45	0.40	0.40	0.45	0.45
10	0.25	0.25	0.25	0.25	0.30	0.30

Time after drug admin (min)	No. of dogs	Mean VFT (volt sec)	Mean difference from 0 time value	Variance	S.E.M.	t	P
0	10	0.39					
15	10	0.39	0			0	N.S.
30	10	0.38	0.01	0.00155	0.012	0.833	N.S.
45	10	0.39	0			0	N.S.
60	10	0.385	0.005	0.00130	0.011	0.45	N.S.
90	10	0.385	0.005	0.00081	0.009	0.55	N.S.

Doses 12.5 mg per kilogram of body wt.

VFT = ventricular fibrillation threshold.

D.F. error not at 1 usually is less than 50 for control and caffeine groups.

was noted at about 45 and 60 minutes when the mean VFT decreased to 0.382 and 0.359 msec from a control value of 0.39 msec ($P < 0.001$) (see Tables I and II and Fig. 3). Similar results were observed in Group B (normal dogs with previously implanted epicardial electrodes) (see Tables III and IV and Fig. 3). There was a statistically significant decrease in ventricular fibrillation threshold at 15, 30, 45 and 60 minutes with a maximum effect at about 45 and 30 minutes (9.6 and 9.2 mV respectively from a control value of 14.6 mV, $p < 0.001$). There was no change in the control experiments (i.e. after the injection of sodium benzoate).

Dogs with experimental myocardial infarction (caffeine and control experiments). The results obtained in this group of dogs are

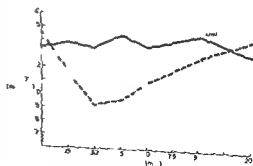


Fig. 3 The effect of caffeine on the VFT of normal dog (impulses delivered through previously implanted epicardial electrodes). There is a decrease in VFT after caffeine administration while there is no change in the controls and in those treated with the combination of caffeine and practolol.

Table IV The effects of caffeine sodium benzoate on the VIT in normal dogs with bipolar implanted electrodes (third to seventh day after implantation)*

Dog	Minutes after intravenous injection						
	0	15	30	45	60	90	120
1	14†	13	—	10	15	15	15
2	13	9	8	10	8	13	12
3	16	9	11	10	11	11	11
4	15	15	6	12	12	15	13
5	10	8	6	6	8	10	10
6	17	17	14	14	13	17	19
7	16	16	12	10	14	11	14
8	15	5	5	5	6	17	17
9	12	12	9	9	8	8	11
10	8	12	12	10	14	18	20

Time after admin of caffeine (min)	No of dogs	Mean VFT (Ma)	Mean difference from 0 time value (Ma)	Variance	SE M	t	P
0	10	14.6					
15	10	11.6	3.0	12.8888	1.135	2.643	0.05
30	10	9.2	5.4	6.2800	0.836	6.459	0.001
45	10	9.6	5.0	6.0000	0.775	6.457	0.001
60	10	10.9	3.7	6.6777	0.817	4.579	0.01
90	10	13.5	1.1	6.5444	0.809	1.360	NS‡
120	10	14.2	0.4				NS

*Dosage 0.25 mg. per kilogram of body weight.

†VFT in milliamperes.

‡Differences not statistically significant.

2.5 msec in duration. The VIT was determined by delivering gated impulses to the right ventricle through the previously implanted bipolar electrodes utilizing a method similar to that of Han.¹⁵ These impulses were programmed using a series of Tektronix waveform and pulse generators which trigger a Grass stimulator (model SD5). At every tenth heart beat this system delivers a series of rectangular pulses of 2.5 msec duration each at intervals of 10 msec. The series of impulses starts immediately after the R wave and ends at the peak of the T wave adequately covering the vulnerable period. The current increased at increments of 1 Ma until ventricular fibrillation was observed (Fig. 1). The current delivered to the dog was measured with a current probe amplifier

and displayed on an oscilloscope. Ten control and 10 caffeine experiments were performed on normal dogs. In addition 5 experiments were done on animals treated by the combination of caffeine sodium benzoate (25 mg. per kilogram of body weight) and prazosin (0.6 mg. per kilogram of body weight).

Results

Control and caffeine experiments on normal dogs. In Group A (intact dogs) no change in the VIT was noted during the 90 minutes following the injection of sodium benzoate. In contrast, after injection of caffeine sodium benzoate a significant decrease in the fibrillation threshold was noted at 15, 30, 45, 60 and 90 minutes after the injection. The maximum effect

Table V Effect of sodium benzoate on the ventricular fibrillation threshold in dogs with acute myocardial infarction (fourth postoperative day)*

Dog	Minutes after intravenous injection					
	0	15	30	45	60	90
1	0.50†	0.45	0.45	0.45	0.45	0.50
2	0.50	0.55	0.55	0.55	0.55	0.50
3	0.45	0.45	0.40	0.40	0.45	0.45
4	0.40	0.45	0.45	0.45	0.40	0.35
5	0.35	0.35	0.35	0.45	0.30	0.30
6	0.20	0.20	0.20	0.20	0.20	0.0
7	0.30	0.30	0.30	0.30	0.30	0.30
8	0.50	0.45	0.45	0.45	0.45	0.50
9	0.45	0.45	0.40	0.40	0.45	0.45
10	0.25	0.25	0.25	0.25	0.30	0.30

Time after drug admin (min)	No of dogs	Mean VFT (wall sec)	Mean difference from 0 time value	Variance	SE M	t	P
0	10	0.39					
15	10	0.39	0			0	NS†
30	10	0.38	0.01	0.00155	0.012	0.833	NS
45	10	0.39	0			0	NS
60	10	0.385	0.005	0.00136	0.011	0.45	NS
90	10	0.385	0.005	0.00081	0.009	0.55	NS

Dosing 12.5 mg per kg gram body wt

VFT 11 sec

Diff. not statistically significant with 5% level of probability

was noted at about 45 and 60 minutes when the mean VFT decreased to 0.382 and 0.359 wsec from a control value of 0.509 wsec ($P < 0.001$) (see Tables I and II and Fig 2). Similar results were observed in Group III (normal dogs with previously implanted epicardial electrodes) (see Tables III and IV and Fig 3). There was a statistically significant decrease in ventricular fibrillation threshold at 15, 30, 45 and 60 minutes with a maximum effect at about 45 and 30 minutes (9.6 and 9.2 Ma respectively from a control value of 14.6 Ma, $p < 0.001$). There was no change in the control experiments (i.e. after the injection of sodium benzoate).

Dogs with experimental myocardial infarction (caffeine and control experiments). The results obtained in this group of dogs are

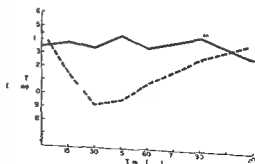


Fig 3 The effect of caffeine on the VFT of normal dogs (impulses delivered through previously implanted epicardial electrodes). There is a decrease in VFT after caffeine administration while there is no change in the controls and in those treated with the combination of caffeine and practolol.

Table V Effect of sodium benzoate on the ventricular fibrillation threshold in dogs with acute myocardial infarction (fourth postoperative day)*

Dog	Minutes after intravenous injection					
	0	15	30	45	60	90
1	0.50†	0.45	0.45	0.45	0.45	0.50
2	0.50	0.50	0.50	0.55	0.55	0.50
3	0.45	0.45	0.40	0.40	0.45	0.45
4	0.40	0.35	0.45	0.45	0.40	0.35
5	0.35	0.35	0.35	0.45	0.30	0.30
6	0.20	0.20	0.20	0.20	0.20	0.20
7	0.10	0.30	0.30	0.30	0.30	0.30
8	0.50	0.45	0.45	0.45	0.45	0.50
9	0.45	0.45	0.40	0.40	0.45	0.45
10	0.25	0.25	0.25	0.25	0.30	0.30

Time after drug admin (min)	No of dogs	Mean VFT (wall sec)	Mean difference from 0 is no value	Variances	SE M	t	P
0	10	0.39					
15	10	0.39	0			0	NS
30	10	0.38	0.01	0.00155	0.012	0.833	NS
45	10	0.39	0			0	NS
60	10	0.385	0.005	0.00136	0.011	0.45	NS
90	10	0.385	0.005	0.00081	0.009	0.55	NS

Dose: 125 mg per kilogram of body weight

VFT: ventricular fibrillation threshold

NS: not statistically significant at the 5% level by the t-test of paired observations.

was noted at about 45 and 60 minutes when the mean VFT decreased to 0.382 and 0.359 wsec from a control value of 0.509 wsec ($P < 0.001$) (see Tables I and II and Fig. 2). Similar results were observed in Group B (normal dogs with previously implanted epicardial electrodes) (see Tables III and IV and Fig. 3). There was a statistically significant decrease in ventricular fibrillation threshold at 15, 30, 45 and 60 minutes with a maximum effect at about 45 and 30 minutes (9.6 and 9.2 Ma respectively from a control value of 14.6 Ma, $p < 0.001$). There was no change in the control experiments (i.e. after the injection of sodium benzoate).

Dogs with experimental myocardial infarction (caffeine and control experiments) The results obtained in this group of dogs are

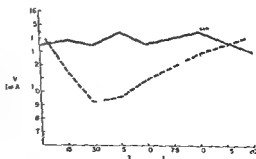


Fig. 3 The effect of caffeine on the VFT of normal dogs (impulses delivered through previously implanted epicardial electrodes). There is a decrease in VFT after caffeine administration while there is no change in the controls and in those treated with the combination of caffeine and practolol.

Table VI Effect of caffeine sodium benzoate on the ventricular fibrillation threshold in dogs with acute myocardial infarction (fourth postoperative day)*

Dog	Minutes after intravenous injection					
	0	15	30	45	60	90
1	0.40†	0.30	0.25	0.25	0.20	0.30
2	0.25	0.20	0.25	0.30	0.30	0.30
3	0.50	0.35	0.30	0.30	0.30	0.30
4	0.40	0.35	0.30	0.30	0.25	0.35
5	0.30	0.25	0.25	0.20	0.20	0.20
6	0.40	0.35	0.35	0.35	0.30	0.35
7	0.60	0.60	0.60	0.55	0.60	0.55
8	0.40	0.40	0.40	0.45	0.45	0.45
9	0.35	0.35	0.30	0.30	0.35	0.35
10	0.30	0.25	0.30	0.30	0.35	0.35
11	0.60	0.60	0.40	0.35	0.35	0.35

Time after admin of caffeine (min)	No of dogs	Mean VFT (wall sec)	Mean difference from 0 time value (wall sec)	Variance	SE V	t	P
0	11	0.409					
15	11	0.364	-0.045	0.0022275	0.0142	3.169	<0.01
30	11	0.327	-0.082	0.00464	0.0206	3.981	<0.01
45	11	0.323	-0.086	0.001046	0.0253	3.399	<0.01
60	11	0.314	-0.095	0.009228	0.0389	3.987	<0.01
90	11	0.332	-0.077	0.008182	0.0273	2.825	<0.01

Dosage 25 mg per kg body weight
 VFT in wall seconds.

given in Tables V and VI and in Fig 2. In the control experiments no significant change in the VFT occurred whereas after caffeine administration the VFT was significantly decreased at 15, 30, 45, 60, and 90 minutes ($p < 0.01$). The maximum effect was noted at 45 and at 60 minutes when the mean VFT decreased to 0.323 and 0.314 wsec, respectively, from a control value of 0.409 wsec. As expected the VFT before the injection of caffeine (0.409 wsec) was lower in dogs with acute myocardial infarction than in normal dogs (0.509 wsec).

Administration of the combinations of caffeine and propranolol and caffeine and practolol. As seen in Table VII propranolol in the dose of 0.2 mg per kilogram of body weight did not significantly affect the VFT. However, when administered simultaneously with caffeine, it prevented the caffeine-induced decrease in VFT. This is

shown in Table VIII, where no change in VFT is observed after the administration of the propranolol-caffeine combination (Fig 4). Similarly, no change in VFT was observed in the dogs treated with caffeine and practolol (Table IX).

Discussion

1. *Values of ventricular fibrillation threshold.* The values of VFT obtained in Group A (intact dogs) are in the range reported by Lown, Kleger, and Williams¹² who employed a similar method. Those obtained in Group B (dogs with previously implanted electrodes) were similar to the results of Han¹³ who utilized a similar technique. There was no change in the VFT in the control experiments. Prolonged anesthesia and repeated determinations did not significantly affect the VFT in the control experiments. This has been reported by

Table II Effect of propranolol on the ventricular fibrillation threshold in intact normal dogs*

Dog	Minutes before (-) and after (+) intravenous injection						
	-15	0	+15	+30	+45	+60	+90
1	0.04	0.10	0.80	0.80	0.00	0.60	0.60
2	0.50	0.50	0.50	0.40	0.50	0.20	0.40
3	0.35	0.35	0.35	0.35	0.35	0.35	0.35
4	0.80	0.80	0.80	0.70	0.90	0.80	0.90
5	0.35	0.35	0.35	0.35	0.40	0.35	0.30

Time after administration of propranolol (min)	No. of dogs	Mean VFT (wall sec)	Mean difference from 0 time control (wall sec)	Variance	STW	t	P
0	5	0.54					
15	5	0.56	+0.02	0.000	0.02	1.0	> 5%
30	5	0.52	-0.02	0.0070	0.038	0.516	> 5%
45	5	0.57	+0.03	0.0020	0.02	1.50	> 5%
60	5	0.57	-0.02	0.0070	0.02	1.0	> 5%
90	5	0.51	-0.03	0.0070	0.038	0.789	> 5%

Dose 0.5 mg per kg body weight
VFT as in sec. data

* Differences not statistically significant

others^{14,15} Although some variation in the control values of VFT between the groups of experiments was observed these differences are not statistically significant.

The effect of caffeine on the VFT of normal dogs. In contrast to the control experiments caffeine produced a significant decrease in the VFT which lasted at least 60 minutes. It is of interest that similar results were obtained with both techniques (Groups A and B). This is important since the accurate determination of VFT is relatively difficult as it is affected by many variables and each technique is characterized by specific advantages and disadvantages.^{16,17} The closed chest technique with impulses delivered through the chest wall of the intact animal involves the problem of the chest wall impedance which might vary from dog to dog or from moment to moment on the same dog, but this technique does offer the advantage of using intact animals without previous operations. On the other hand the technique utilizing implanted electrodes bypasses the problem

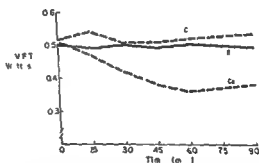


Fig. 4 The effect of propranolol on the caffeine induced decrease of VFT in normal dogs. Note that there is no decrease in VFT after the administration of the combination of caffeine and propranolol.

of variable impedance as well as the open chest problem but introduces the factor of electrode implantation, clot formation or myocardial reaction around the implanted electrode. Open-chest techniques were avoided in this study since they introduce important physiological alterations.

3 Effect of caffeine on the VFT of dogs

Table VIII Effect of the combination of caffeine sodium benzoate plus propranolol on the atricular fibrillation threshold in intact normal dogs*

Dog	Minutes before (-) and after (+) intravenous injection						
	-15	0	+15	+30	+45	+60	+90
1	0.30†	0.30	0.35	0.35	0.35	0.35	0.35
2	0.45	0.45	0.45	0.45	0.50	0.45	0.45
3	0.30	0.30	0.30	0.25	0.30	0.30	0.30
4	0.75	0.70	0.75	0.70	0.75	0.75	0.75
5	0.80	0.80	0.80	0.80	0.80	0.80	0.80
6	0.70	0.70	0.80	0.70	0.60	0.60	0.60
7	0.60	0.60	0.70	0.60	0.60	0.60	0.60
8	0.40	0.40	0.30	0.30	0.40	0.40	0.40
9	0.35	0.35	0.40	0.40	0.40	0.40	0.40

Time after drug admin (min)	No. of dogs	Mean VFT (wall sec)	Mean difference from 0 time control (wall sec)	Variance	SE M	t	P
0		0.511					
15	9	0.539	+0.078	0.00382	0.0205	1.356	NS†
30	9	0.506	0.005				NS
45	9	0.506	0.005				NS
60	9	0.516	0.005				NS
90	9	0.516	0.005				NS

*Dosage caffeine sodium benzoate = 25 mg per kilogram of body weight; dosage propranolol = 0.2 mg per kilogram of body weight.

†VFT in wall seconds.

‡Differences not statistically significant.

with acute myocardial infarction. The VFT of dogs with acute myocardial infarction was lower than that of normal dogs. During the fourth day after coronary ligation the heart muscle manifests the characteristic pathology of acute myocardial infarction and one would anticipate that the VFT would be below normal. These results are in agreement with observations of others who observed significant decrease in the VFT in ischemic hearts.^{16,22,23} In dogs with acute myocardial infarction the VFT which had been lowered because of ischemia was further decreased by caffeine. This might conceivably facilitate the development of spontaneous ventricular fibrillation (and sudden death) when myocardial ischemia and caffeine are operating simultaneously.

4. The effect of the combination of caffeine and beta blocking agents on the VFT. As has been reported by others, propranolol (0.2

mg per kilogram of body weight) did not affect the VFT to any significant degree.²⁴ However, propranolol probably prevented the caffeine induced decrease in VFT when administered simultaneously with it. This effect is related to the beta blocking action of propranolol rather than to its quinidine like effect since similar results were obtained by the use of pindolol and pure beta blocking agents which do not have significant direct action on the cardiac muscle. The dogs receiving this combination behaved similarly to the controls. These results would suggest that the effect on the fibrillation threshold may be mediated directly or indirectly through the adrenergic mechanism. It has been shown that sympathetic nerve stimulation results in an accentuation of asynchrony of recovery of the myocardial excitability leading to a marked decrease in VFT. Exogenous catecholamine administration has the same

Table IX. Effect of the combination of caffeine sodium benzoate plus practolol on the ventricular fibrillation threshold in normal dogs with bipolar implanted electrodes (third to seventh day after implantation)*

Dog	Minutes after intravenous injection						
	0	15	30	45	60	90	120
1	9†	10	11	11	10	10	11
2	11	11	10	9	9	9	9
3	17	11	12	12	12	11	11
4	8	7	7	8	7	8	11
5	12	11	13	13	12	12	10

T 10 after drug admin (min)	No of dogs	Mean VFT (Mo)	Mean difference from 0 time value (Ma)	Variance	S.E. V	t	P
0	5	10.4					
15	5	10.2	0.2	0.10	0.38	0.53	NS†
30	5	10.6	0.2	1.70	0.59	0.33	NS
45	5	10.6	0.2	2.20	0.67	0.30	NS
60	5	10.0	0.4	1.30	0.51	0.78	NS
90	5	10.0	0.4	1.30	0.51	0.78	NS
120	5	10.4	0.0				NS

Dose of sodium benzoate = 25 mg per kg of body weight; dose of practolol = 0.6 g per kilogram of body weight. VFT in voltage. Difference statistically significant at the 5% level by a paired comparison.

effect in the initial 10 to 10 minutes after administration.¹¹ Since caffeine results in stimulation of adrenergic activity,^{6,8} it may decrease the VFT through this mechanism.

Mechanism of decrease of VFT by caffeine. Caffeine has many pharmacologic effects which might be anticipated to affect the VFT. These include adrenergic stimulation, direct myocardial stimulation with increases in cardiac output, contractility, cardiac work, oxygen uptake, and coronary AV difference. Agents such as catecholamines and digitalis¹¹⁻¹³ producing similar effects are usually associated with depression of the VFT. A mechanism by which caffeine decreases the VFT is the adrenergic stimulation mentioned above. The prevention of the caffeine-induced decrease in VFT by propranolol or practolol supports this view. The elevation of serum free fatty acid levels after caffeine administration may contribute to this effect.¹² A rela-

tion between serum free fatty acids and arrhythmias and death after acute myocardial infarction has been reported by a group of investigators. In addition, caffeine increases intracellular 3',5'-cyclic AMP by inhibiting phosphodiesterase, elevates serum adrenal steroid levels, and probably directly affects the action potential.^{10,11} The factors mentioned above singly or collectively could result in facilitating the development of re-entry which under certain conditions might lead to ventricular fibrillation.

The effect of caffeine on calcium may also play a role. Caffeine decreases the calcium binding which may lead to an increased concentration of calcium in the cell.⁹ Calcium was found to cause a reduction in the maximum rate of rise of the action potential which can slow the velocity of impulse propagation and shorten the refractory period. These effects would favor the development and maintenance of re-entrant excitation and possibly

fibrillation.⁶ Under certain conditions caffeine may initiate ventricular fibrillation.¹²

Summary

The effect of caffeine administration on the VFT was studied in normal dogs and in dogs with acute myocardial infarction. Two methods were employed: the first utilized impulses delivered through the chest wall of the intact animal and the second used epicardial electrodes implanted four to seven days previously.

Caffeine produced a decrease in VFT starting 15 minutes after injection and this effect lasted about 60 minutes.

Propranolol and pindolol prevented the caffeine induced decrease of VFT.

In dogs with acute myocardial infarction the VFT was lower than normal and was further decreased after caffeine administration.

Although the dose of caffeine utilized in this study is higher than that usually consumed by humans, it is possible that lower doses have a significant effect when combined with other agents. The various factors that affect the VFT which might have arrhythmogenic effects are presently under study. There is suggestive evidence that a number of factors might be cumulatively significant in susceptible individuals. These factors may include cigarette smoking, various degrees of stress effects due to anxiety and exertion, various drugs—i.e., isoproterenol, ephedrine and several sympathomimetic agents and caffeine. The role of caffeine requires further study in this regard.

REFERENCES

1. Bellet S, Kershbaum A and Aspe J. The effect of caffeine on free fatty acids. *Arch Intern Med* 116:750 1965.
2. Bellet S, Kershbaum A and Finck J M. Response of free fatty acids to coffee and caffeine. *Metabolism* 17:702 1968.
3. Bellet S, Kostis J B, Roman L and DeCastro O. Effect of coffee ingestion on adrenocortical secretion in young men and dogs. *Metabolism* 18:1007 1969.
4. DeSchaepe-dryver A F. Physiopharmacological effects on suprarenal secretion of adrenaline and noradrenaline in dogs. *Arch Int Pharmacodyn Ther* 119:517 1959.
5. Levi L. The effect of coffee on the function of the sympatho-adreno medullary system in man. *Acta Med Scand* 181:431 1961.
6. Bellet S, Roman L, DeCastro O, Kershbaum A and Kershbaum A. Effect of caffeine ingestion on catecholamine release. *Metabolism* 18:789 1969.
7. Kershbaum A, Kershbaum R, Carter R I, Bellet S and Feinberg L. The free catecholamines in the free fatty acid response to cigarette smoking. *Circulation* 28:57 1963.
8. Kershbaum A, Bellet S, Jimenez J and Feinberg L J. Difference in effects of caffeine and cigarette smoking on free fatty acid oxidation and catecholamine excretion. *JAMA* 195:1095 1966.
9. Grollman A and Grollman E F. Pharmacology and therapeutics. 4th ed. Lea & Febiger, Philadelphia 1970 p 701.
10. Sutherland I W, Robinson G A and Boulton R W. Some aspects of the biological role of adenosine 3',5' monophosphate (cyclic AMP). *Circulation* 37:219 1968.
11. Han J, Defalon P G and Moe G B. Adrenergic effects on ventricular vulnerability. *Circ Res* 14:516 1964.
12. Crumbich I, Howard S W and Morita V I. Factors related to the initiation of ventricular fibrillation in the isolated heart. Effects of calcium and potassium. *Circ Res* 4:42 1954.
13. Town B, Kleiger R and Williams J. Cardioversion and digitalis drugs. Changed threshold to electric shock in digitalized animals. *Circ Res* 17:519 1965.
14. Harris A S. Delayed development of ventricular ectopic rhythms following experimental coronary occlusion. *Circulation* 11:118 1950.
15. Han J. Ventricular vulnerability during acute coronary occlusion. *Am J Cardiol* 24:42 1969.
16. McIntosh H D, Stamer F and Whaler R F. A comparison of the electrical ventricular fibrillation threshold with and without anesthesia. *Am Heart J* 72:419 1966.
17. Brenner M. Bretylium tosylate for suppression of induced ventricular fibrillation. *Am J Cardiol* 17:528 1966.
18. Tibbels C M, Levy L M and MacLear L D. The influence of temperature and coronary occlusion on the ventricular fibrillation threshold. *Surg Gynecol Obstet* 109:914 1959.
19. Vintzios R A and MacLear L D. Ventricular fibrillation threshold. *Am J Physiol* 201:457 1961.
20. Lumball A D, MacLear L D, DeWitt A R and Demers K. The influence of hyperbaric oxygen and of hypoxia on the ventricular fibrillation threshold. *J Thorac Cardiovasc Surg* 50:342 1965.
21. Cerletti H, Flennig W H and Malm J R. A quantitative evaluation of the effects of acidosis and alkalosis upon the ventricular fibrillation threshold. *Surgery* 59:1050 1966.
22. Wiggers C J, Wiggers R and Liners B. The effects of myocardial ischemia on the

- fibrillation threshold—The mechanism of spontaneous ventricular fibrillation following coronary occlusion *Am J Physiol* 131:309 1940
- 23 Shumway N E Johnson J A and Stish R J The study of ventricular fibrillation by threshold determinations *J Thorac. Cardiovasc Surg* 34 643 1957
- 24 Rosati R A Alexander J A Wallace A G Sealy W C and Young W G Failure of beta adrenergic blockade to alter ventricular fibrillation threshold in the dog *Circ Res* 19 721 1966
- 25 Hoffman B F Siebens A V Crisfield P F and Brook C McC The effect of epinephrine and norepinephrine on ventricular vulnerability *Circ Res* 3 140 1955
- 26 Lown H and Cannon R Electrical stimulation to estimate the degree of digitalization *Am J Cardiol* 22:251 1968
- 27 de Gubareff T and Sleator W Effects of caffeine on mammalian atrial muscle and its interaction with adenosine and calcium *J Pharmacol Exp Ther* 148 202 1965
- 28 Temple S V and Davis L D Effect of calcium concentration on the transmembrane potentials of Purkinje fibers *Circ Res* 20 31 1967

Antinuclear antibody response to procainamide in man and laboratory animals

Sen, a Whittingham, MB, Ch B, DCP, PhD

Ian R Mackay MD, FRCP, FRACP

Judith 1 Whitworth MB, MRACP

Gracie Sloman, M B B Sc 1 R C P (Ldip), 1 A 1 C P

M R C P (Lond) I 1 C C

Victoria Australia

In the past ten years a clinical syndrome with features of systemic lupus erythematosus (SLE) including positive tests for LL cells and antinuclear antibody has become recognized as an adverse side effect of procainamide¹. The use of procainamide for the treatment of cardiac arrhythmias particularly those occurring after myocardial infarction has resulted in the syndrome of 'procainamide lupus' becoming more frequently recognized. The syndrome has features of an autoimmune process but its mode of induction is unknown. We report a prospective study on the induction of antinuclear antibody (ANA) in patients treated with procainamide. Laboratory animals were given procainamide for 6 months or longer. Although over a quarter of the treated patients developed high titer ANA none of the animals tested responded in this manner.

Materials and methods

Patients The potential patients 199 in number, were those admitted to a coronary

care unit over a 12 month period, and those who received procainamide as therapy for cardiac arrhythmias 48 in number entered the study. Those from whom at least three samples of sera were available at minimum intervals of one month, comprised the case material of this study. These comprised 25 men and four women aged from 31 to 76 years from these 160 were tested and sera were available from 15 before procainamide was started.

Animals Ten rabbits 10 guinea pigs 20 Wistar rats 40 Hall Institute (HI) outbred closed colony mice and 20 inbred New Zealand Black (NZB) mice were given procunumude by subcutaneous injection three times a week for 30 weeks. The NZB mice were known to develop positive tests spontaneously for antirathyroid and anti-nuclear autoantibodies; they were included to test for enhanced development of ANA by procunumude. Other groups of animals were outbred and from closed colonies. Animals within each group were of the same age and the groups other than the guinea

[illegible]

pigs which were males contained in equal number of males and females. The dose of procainamide injected subcutaneously was equivalent to 10 times the conventional daily dose of 2 Gm for an average 10 kilogram man converted to grams per kilogram of body weight of the animal but the drug was given only three times per week instead of daily. No adjustment was made for gain in weight of the animals during the experiment.

Sera tested for antinuclear antibodies were obtained before procainamide was commenced and thereafter at 10, 20 and 30 weeks; two of three of the surviving animals were killed on completion of the 30 week course of procainamide and the remainder six months later. Tissues from kidney, heart, lung and skin were processed for examination for deposited globulins by immunofluorescence; tissues from kidney, thymus, lung, heart, liver, spleen, pancreas, stomach, duodenum and skin were processed for histological examination.

Controls. Controls for patients were blood donors and members of elderly citizens clubs matched for age and sex with the patients and not receiving procainamide. Controls for mice were 20 H1 mice and 10 NZB mice matched for age and sex with the test mice and given 0.1 ml of saline subcutaneously three times a week for 30 weeks.

Tests for antinuclear antibodies. Sera from patients and all animals were tested by immunofluorescence for ANA reactive with granulocyte and lymphocyte nuclei in smears of human blood² and sera from guinea pigs and mice were tested also for ANA using air dried 4μ frozen sections of rat liver. Rabbit antiserum to human globulin and goat antiserum to rabbit globulin were prepared in our laboratory³ and conjugated with fluorochrome isothiocyanate (FICT) and goat antisera to guinea pig globulin, mouse globulin and rat globulin conjugated with FICT were obtained from the Nutritional Biochemical Corporation, U.S.A. Sera containing antinuclear antibodies were titrated in tenfold dilutions of 0.05 per cent bovine serum albumin in phosphate buffered saline, pH 7.3. Blood samples from four patients with high titer ANA reactions were tested for LE cells by the method of Mignath and Winkle.⁴

Absorption studies. Samples of human serum (0.2 ml) which contained ANA in high titer were mixed with amounts of procainamide varying from 1 to 100 mg, held at 4°C for 24 hours, examined for precipitation and centrifuged at 40,000 g; the sera then were tested for ANA.

Results

Patients. Antinuclear antibodies were detected in 24 of 29 (83 per cent) of the patients given procainamide in titers up to 1:1000 (Table I) and in six of 29 (20 per cent) age sex matched controls in titers up to 1:10. A titer of ANA of 10 or greater was obtained in 18 of 29 (62 per cent) of the patients and in two of 29 (7 per cent) of the controls and in six patients but none of the controls the titer was equal to or greater than 1:100 (Fig. 1). Blood from four patients with a high titer of ANA ($\geq 1:100$) was tested for LE cells and gave a positive result. The occurrence of ANA in patients given procainamide was not directly dependent on the dose nor on the age of the patient. Conversion occurred three to six months after commencement of treatment. In four patients tested serially after procainamide was stopped the titer of ANA fell.

Of the 160 sera tested, 89 gave a positive test for ANA and 68 (76 per cent) gave the same titer with nuclei of lymphocytes and granulocytes. Pretreatment serum from two patients reacted only with granulocyte nuclei but during treatment reacted equally with both granulocyte and lymphocyte nuclei to titers of 10 and 100.

Animals

MORBIDITY AND MORTALITY. All animals injected with procainamide developed indolent ulcers at the site of injection and one rabbit developed generalized dermatitis. There was a high mortality rate while procainamide was being given in the rabbits (7 of 10), guinea pigs (4 of 10), the H1 mice (31 of 40) and the NZB mice (20 of 20) but not in the rats (1 of 20). The mortality rate in the control mice given saline for a comparable period was lower for the H1 mice being 2 of 20 and the NZB mice 3 of 10. Some animals died immediately after injection and others were found dead in their cages. The cause of death was not determined.

Table 1 Peak titer of antinuclear antibodies in patients given procainamide (P 1)

Age (yr)	Daily dose (Cm)	Duration of P 1 (mo)	Peak titer	Time (mo)*
<i>Men</i>				
59	2.0	3	0	
58	2.0	3	0	
	0.25	3		
62	2.0	6	0	
		12		
43	2.0	30	0	
50	2.0	3	1	3
55	2.0	6	1	3
39	2.0	7	1	5
50	1.0	6	1	3
	2.0	3		
56	2.0	9	1	9
55	2.0	12	1	9
31	2.0	3	10	3
60	2.0	5	10	5
58	2.0	1		
	1.0	5	10	3
16	1.5	1		
	0.75	2	10	1
	0.5	2		
16	2.0	6	10	2
62	1.5	4	10	5
	2.0	4		
72	2.0	9	10	6
65	1.0	9	10	7
44	2.0	9	10	6
46	2.0	9	10	5
65	2.0	11	10	11
45	2.0	6	100	6
71	2.0	9	100	4
54	1.0	9	100	5
72	2.0	7	1 000	7
<i>Women</i>				
35	1.5	6	0	
76	1.0	9	10	3
53	1.5	7	100	7
51	1.5	14	1 000	15

*F 10 to reach peak titer

DEPOSITS None of 10 rabbits and 20 rats given procainamide had a positive ANA test. Two of 10 guinea pigs had a transient weak "speckled" reaction. The incidence of positive tests before and during administration of procainamide was, for the 40 III mice, 5 and 66 per cent and for the 20 NZB mice, 0 and 50 per cent. However, the occurrence of ANA in these mice could not be attributed to procainamide in that the incidence of positive tests for ANA during administration of saline in control III mice rose similarly from 10 to 70 per cent and in control NZB mice from nil to 87 per

cent (Table II). The kidneys of three guinea pigs examined showed patchy, linear deposits of globulin of uncertain significance in the glomeruli. The kidneys of seven III mice and four NZB mice injected with procainamide showed granular deposits in glomeruli; however, similar deposits were present in the glomeruli of the control 16 III mice and 1 NZB mouse, indicative of the spontaneous occurrence of "immune complex" nephritis in both the experimental and control groups. The heart and lungs of all animals tested were free of immune deposits.

Table II Serum antinuclear antibodies (1N1) in animals treated with procainamide (PA) and their controls

Animal	No. 1N1 +ve/No. living				
	Before PA	During PA			After PA 56 weeks
		10 weeks	20 weeks	30 weeks	
Rabbit (10)	0/10	0/9	0/5	0/3	NT
Guinea pig (10)	1/10	2/9	0/7	0/6	NT
Cats (9)	0/10	0/10	0/0	0/10	NT
H1 mice (40)	7/40	9/40	11/14	6/9	NT
Control (20)	2/10	10/10	11/18	17/17	14/16
NZB mice (10)	0/10	1/10	2/6	0	0
Control (10)	0/10	3/10	7/8	3/5	1/1

NT Not tested.

HISTOLOGY. Autopsies were performed on 26 of 40 H1 mice, 6 of 20 NZB mice, 14 of 20 rats, 5 of 10 guinea pigs and 4 of 10 rabbits given procainamide.

Mice. Membranous glomerular lesions were seen in seven H1 mice and two NZB mice and cortical lymphoid aggregates in six H1 mice and one NZB mouse. These changes were equivalent to those seen in controls injected with saline. Changes in the liver consisting of hepatic cell steatosis and vacuolation and portal infiltrates seen in 11 H1 mice and 4 NZB mice were considered to be nonspecific and the pulmonary changes of alveolar thickening and/or lymphoid foci in 19 H1 mice and four NZB mice were attributed to infection but tissues were not cultured.

Rats. In all 14 there were varying degrees of pulmonary alveolar thickening, fibrosis or consolidation attributed to infection. Other organs were unremarkable.

Guinea pigs. In four there were collections of lymphoid cells in the kidney and lungs and fatty vacuolation in the liver. These changes were considered to be nonspecific.

Rabbits. There were in the four rabbits examined occasional lymphoid foci in the kidney, marked pulmonary alveolar thickening and collections of eosinophilic leukocytes in various organs.

The glomerular lesions in the mice could

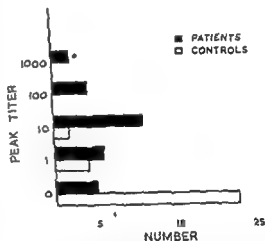


Fig 1 Antinuclear antibodies were detected in 24 of 29 patients given procainamide and 6 of 29 matched controls. Peak titers of 10 or greater were detected in 18 patients and the 4 patients with high titers who were tested for LE cell, all gave a positive result ().

be related to spontaneously occurring autoimmune (antinuclear) reactions which develop in both NZB and H1 mice. In none of the other species examined were there changes suggestive of lesions of human lupus erythematosus.

Absorption studies. No precipitin reaction was detected between human serum containing procainamide induced antinuclear

antibody and procunamide and there was no reduction in titer of antinuclear antibody after positively reacting sera were absorbed with procunamide.

Discussion

Two surveys in Sweden and New York gave a prevalence of SLE in the population of about one per 10 thousand⁶ it can therefore be considered a rare disease in human beings. The occurrence of a lupus like syndrome in patients treated with procunamide is generally considered to be more frequent than this but a precise figure is not known because no data are available for a large population at risk, moreover there would be problems of disease definition in such a study because drug induced lupus is milder than the natural disease. However, if the occurrence of ANA in high titer be taken as the 'pro-drome' of drug induced lupus then serological studies on groups treated with procunamide give some indications of the risk, the higher proportion (83 per cent) with ANA in our study than in others (50 to 60 per cent)⁷⁻⁹ may be attributed to the source of nuclei we used to detect ANA.

Most of the patients who developed ANA after procunamide did so within three to six months, six had peak titers of 100 to 1 000 and four had a positive test for LE cells. Whether differences in time of onset and titer of antinuclear antibody were related to differing rates of acetylation of the drug¹⁰ was not ascertained in our study. It might be said that the few high titer reactors to procunamide in our series would be equivalent to those hypersensitive subjects identified by Worledge and associates¹¹ as being highly sensitive to the immunological side effects of alpha methyl dopa. With this latter drug some 20 per cent of patients developed a positive Coombs test which was dose and time dependent but no hemolysis while a few became 'exquisitely sensitive' and presented acutely with overt hemolysis.

None of the animals we studied developed evidence of an autoimmune response to procunamide despite parenteral administration for 30 weeks, nor was there augmentation of the spontaneous development of antinuclear antibodies in mice. A finding

of some incidental interest was the high spontaneous incidence of ANA in our outbred Hill Institute mice a property hitherto studied mostly in the 'New Zealand' strains.¹ It appears that a predisposition to develop autoimmune reactions to nuclear antigens may hold for mice in general and, as well, in some strains a drug, hydralazine, has enhanced the natural occurrence of antinuclear reactions.¹²

Our failure to induce an analogue of human procunamide lupus in various animals is in keeping with findings of Dubois and Strain¹³ who despite assiduous efforts likewise failed with small laboratory animals mongrel dogs, minipig and a *Macaca fusata* monkey given prolonged and high doses of the drug together with solar exposure. We endorse Dubois' speculation "whether etiologic studies of lupus in the animal are truly applicable to the human form of the disease".

It is difficult to envisage how drugs for example alpha methyl dopa and procunamide cause production of autoimmune-type antibodies. In particular neither our present investigations nor those by Worledge and colleagues¹¹ on effects of alpha methyl dopa, nor those by Ellman and colleagues¹⁴ with hydralazine in guinea pigs give the slightest evidence that the drug acts as a haptén or in any way influences the specificity of the resulting autoantibodies.

We therefore turn to speculations by Burnet¹⁵ about the nature of the alpha methyl dopa effect which have recently been applied also to the procunamide results.¹⁶ These are based on his concept that soon after differentiation all immunocytes are subject to a censorship which eliminates functionally or physically those cells which react significantly with accessible body antigens. Where the receptor combining site has a borderline reactivity with a 'self' antigenic determinant the 'decision' between elimination and proliferation given at first contact will be influenced by many factors. These include genetic ones associated with a heightened resistance to allogeneic effects as in NZB mice,¹⁷ the concentration and mode of presentation of the antigen which can be combined as effective concentration, any relevant somatic mutation which may have occurred

Table III Postulated determinants of origin of pathogenic forbidden clones in autoimmune disease and drug induced autoimmune syndromes

Mutation		Drug (alpha methylidopa procainamide hydralazine)	Result
Germ line	Somatic		
+	++	-	SLI or AHA
+	+	-	} Positive antinuclear antibody or Coombs test no disease
-	++	+	
-	+	+	
-	++	+	Mild disease
+	+	+	SLI or AHA

HALE, 10 m 1 p a erythematous AHA 1 m m m been 15 c nemia

in individual cell lines and any significant influence of a drug on the microenvironment in which the decision is made

In the absence of a drug effect one might postulate that the pathogenic clone in a patient with clinical autoimmune disease and autoantibody has three genetic changes a b c not present in immunocytes of a normal individual. The mutations may be germ line or somatic—one for example a is probably always of germ line origin and others b and c could be somatic (Table III) there seems required a minimum of three functional changes but the possibility exists that the same position might be reached in a variety of ways e.g. with more than three genetically based changes of lesser extent or with internal environmental factors playing a greater part

In Table III each of the mutations is regarded as equivalent and indicated as +. The effect of the drug also shown as + can be regarded either as (1) inducing a phenocopy of a somatic mutation or (2) shifting the level of decision between tolerance and proliferation. Such a formulation is obviously valid only if Burnet's stochastic forbidden clone approach to the interpretation of autoimmune disease is accepted; however it is not considered easy to offer any alternative persuasive interpretation of autoimmunity in terms of either the viral infection or altered antigen theories of autoimmune disease.

It may be of more than passing interest

that the three major drugs which are presumed to have this significant influence on the microenvironment in which tolerance immunity decisions are made are each effective in the therapy of hypertensive cardiovascular disease: alpha methylidopa, procainamide and hydralazine.

Summary

A prospective study of 29 patients given procainamide showed that 83 per cent of patients vs 20 per cent of 29 age and sex matched controls gave positive tests for antinuclear antibody (ANA). Six patients (20 per cent) four of whom had LE cells developed high titer ANA of the lupus-type. The induction of ANA was independent of the dose of procainamide given, the duration of treatment and the age of the patient. Titers fell after procainamide was discontinued.

ANA could not be induced in rabbits, guinea pigs, rats and mice injected with procainamide for 30 weeks nor was there enhancement of the naturally occurring age related development of ANA in mice.

The development of ANA in high titer which we take as the prodrome of drug induced lupus erythematosus can be expected in one in five patients treated with procainamide irrespective of the dose given. Our understanding of the mechanism of drug induced forms of lupus may be furthered more by studies in man than in the apparently resistant laboratory animal.

antibody and procunimide, and there was no reduction in titer of antinuclear antibody after positively reacting sera were absorbed with procunimide.

Discussion

Two surveys in Sweden and New York give a prevalence of SLE in the population of about one per 10 thousand^{5,6}; it can therefore be considered a rare disease in human beings. The occurrence of a lupus-like syndrome in patients treated with procunimide is generally considered to be more frequent than this, but a precise figure is not known because no data are available for a large population at risk; moreover there would be problems of disease definition in such a study because drug-induced lupus is milder than the natural disease. However if the occurrence of ANA in high titer be taken as the "pro-drome" of drug-induced lupus then serologic studies on groups treated with procunimide give some indications of the risk: the higher proportion (83 per cent) with ANA in our study than in others (50 to 60 per cent)⁷⁻⁹ may be attributed to the source of nuclei we used to detect ANA.

Most of the patients who developed ANA after procunimide did so within three to six months; six had peak titers of 100 to 1,000 and four had a positive test for LE cells. Whether differences in time of onset and titer of antinuclear antibody were related to differing rates of metabolism of the drug¹⁰ was not ascertained in our study. It might be said that the few high titer reactors to procunimide in our series would be equivalent to those hypersensitive subjects identified by Worledge and associates¹¹ as being highly sensitive to the immunologic side effects of alpha-methyl-dopa. With this latter drug some 20 per cent of patients developed a positive Coombs' test which was dose and time dependent but no hemolysis while a few became 'exquisitely sensitive' and presented acutely with overt hemolysis.

None of the animals we studied developed evidence of an autoimmune response to procunimide despite parenteral administration for 30 weeks, nor was there augmentation of the spontaneous development of antinuclear antibodies in mice. A finding

of some incidental interest was the high spontaneous incidence of ANA in our outbred Haff Institute mice a property hitherto studied mostly in the New Zealand strains.¹² It appears that a predisposition to develop autoimmune reaction to nuclear antigens may hold for mice in general and, as well, in some strains a drug, hydralazine, has enhanced the natural occurrence of antinuclear reactions.¹³

Our failure to induce an analogue of human 'procunimide lupus' in various animals is in keeping with findings of Dubois and Strum¹⁴ who despite assiduous efforts, likewise failed with small laboratory animals: mongrel dogs, a miniature and a *Macaca fusata* monkey given prolonged and high doses of the drug together with solar exposure. We endorse Dubois' speculation "whether etiologic studies of lupus in the animal are truly applicable to the human form of the disease."

It is difficult to envisage how drugs for example alpha-methyl-dopa and procunimide cause production of autoimmune-type antibodies. In particular, neither our present investigations nor those by Worledge and colleagues¹¹ on effects of alpha-methyl-dopa nor those by Ellman and colleagues¹⁵ with hydralazine in guinea pigs give the slightest evidence that the drug acts as a hapten or in any way influences the specificity of the resulting autoantibodies.

We therefore turn to speculations by Burnet¹⁶ about the nature of the alpha-methyl-dopa effect which have recently been applied also to the procunimide results.¹⁷ These are based on his concept that soon after differentiation all immunocytes are subject to a censorship which eliminates functionally or physically those cells which react significantly with accessible body antigens. Where the receptor combination has a borderline reactivity with a self-antigenic determinant the decision between elimination and proliferation given at first contact will be influenced by many factors. These include genetic ones associated with a heightened resistance to toxicologic effects as in N/B mice¹⁸ the concentration and mode of presentation of the antigen which can be combined as effective concentration, any relevant somatic mutation which may have occurred

Diagnosis and treatment of a case of recurrent ventricular tachycardia

William H Barry MD

Edwin L Alderman MD

Pat O Daily MD

Donald C Harrison MD FACC
Stanford Calif

The deficiencies of standard electrocardiographic and clinical criteria in distinguishing ventricular tachycardia from junctional or supraventricular tachycardia with aberrant QRS complexes have recently been emphasized.^{1,2} Because of differences in prognostic implications and in medical and surgical treatments of these conditions this distinction has considerable practical importance. We recently have studied a patient suffering from recurrent refractory tachycardia in whom the techniques of atrial recording, competitive atrial pacing and Holter Recorder monitoring were helpful in establishing a diagnosis of ventricular tachycardia. An accurate diagnosis in this patient permitted subsequent major diagnostic and therapeutic procedures which resulted in control of his arrhythmia.

Case report

R. Z. SLH No 33-30-54 a 62 year old Caucasian, retired Stanford University Hospital for the last time on July 24, 1970 because of recurrent tachycardia. The patient had been well until 1959 when he suffered an inferior myocardial infarction.

Following an uneventful recovery he did well until 1961 when he developed paroxysmal tachycardia with aberrant QRS complexes which was terminated by intravenous vasopressors. He was begun on quinidine. Aside from an episode of chest pain diagnosed as pericarditis and treated with a course of steroid in 1962 he did well until July 26, 1969 when tachycardia recurred. An electrocardiogram (ECG) taken at that time demonstrated a ventricular rate of 194 per minute and wide aberrant QRS complexes (Fig 1 A). A diagnosis of ventricular tachycardia was made and the patient was cardioverted to normal sinus rhythm (Fig 1 B). On Aug 2, 1969 a tachycardia recurred. In comparison with the previous tachycardia the rate was slightly slower at 180 per minute and the QRS complexes had a different configuration (Fig 1 C). This tachycardia was converted to normal sinus rhythm by the administration of intravenous neosynephrine; and subsequent arrhythmias were thought to be supraventricular tachycardias with aberration. Despite treatment with a variety of antiarrhythmic agents including procainamide, propranolol, digoxin, diphenylhydantoin and quinidine alone and in combinations adequate prevention of this recurrent arrhythmia was not achieved. From August 1969 to July 1970 he had 11 documented episodes of tachycardia. With one exception which was converted with neosynephrine and had an ECG pattern identical to that shown in Fig 1 C all these arrhythmias were resistant to vagal maneuvers, required electrical reversion and had the same ECG pattern.

From the Department of Cardiology and Cardiac Surgery, Stanford University School of Medicine, Stanford, Calif 94305.

This work was supported in part by a National Institute of Health Grant, Nos. HE-09058, HE-5 09 and HE-05866 and grants from the American Heart Association, No. 67-708.

Received for publication February 15, 1971.

Revised manuscript accepted by Donald C. Harrison, MD, Chief, Cardiology Division, Stanford University School of Medicine, Stanford, Calif 94305.

We thank Sir Macfarlane Burnet for helpful theoretical discussion, Sister I Linford, Sister I Hurley and the staff of the Coronary Care Unit of The Royal Melbourne Hospital for their help with patients, and Miss Julie Robson for excellent technical assistance. We are indebted to Drs N McCarthy and A Jenkins of E. R. Squibb & Sons for supplies of procainamide for use in experimental animals.

REFERENCES

- 1 Fidd A F Procainamide induced lupus erythematosus. *N Engl J Med* 267:1357 1962
- 2 Dubois L E Procainamide induction of a systemic lupus erythematosus like syndrome. *Medicine (Baltimore)* 48:217 1969
- 3 Whittingham S and Mickey J R Laboratory methods for diagnosis of autoimmune disease. *Med J Aust* 1:1200 1969
- 4 Magath T B and Winkle V Technique for demonstrating LE (lupus erythematosus) cells in blood. *Am J Clin Pathol* 22:586 1952
- 5 Leonhardt F Family studies in systemic lupus erythematosus. *Acta Med Scand* 176 Suppl 416 1964
- 6 Siegel M Lee S L and Peress N S The epidemiology of drug induced systemic lupus erythematosus. *Arthritis Rheum* 10:407 1967
- 7 Blomgren S I Condemi J J Bignall M C and Vaughan J H Antinuclear antibody induced by procainamide. *N Engl J Med* 281:64 1969
- 8 Klijman M Cimin Belsky N Kamich A and Ben Elfrum S Occurrence immunoglobulin pattern and specificity of antinuclear antibodies in sera of procainamide treated patients. *Clin Exp Immunol* 7:641 1970
- 9 Molnar J Dubois L E Blitch M Bland S I and Friou G J Procainamide-induced serologic changes in asymptomatic patients. *Arthritis Rheum* 12:608 1969
- 10 Dreyfuss J Bigger J T Jr and Schreier E C Biotransformation of procainamide in man and the monkey and of N acetylprocainamide in the monkey. *Clin Pharmacol Ther* 12:289 1971
- 11 Worledge S M Carstairs K C and Dacie J V Autoimmune haemolytic anemia associated with α methyl dopa therapy. *Lancet* 1:1966
- 12 Norins I C and Holmes M C Antinuclear factor in mice. *J Immunol* 93:148 1964
- 13 Cannat A and Seligmann M Induction of isoniazid and hydralazine of antinuclear factors in mice. *Clin Exp Immunol* 3:99 1968
- 14 Dubois F L and Strain L Failure of procainamide to induce a systemic lupus erythematosus like disease in animals. *Toxicol Appl Pharmacol* 22:751 1972
- 15 Ellman I Inman J and Green I Strain difference in the immune response to hydralazine in inbred guinea pigs. *Clin Exp Immunol* 9:927 1971
- 16 Burnet F M Cellular immunology. Melbourne 1969 Melbourne University Press
- 17 Burnet F M Autoimmunity and autoimmune disease. Oxford 1972 Medical and Technical Publishing Company Ltd
- 18 Staples P J and Fath N Relative inability to induce tolerance in adult NZB and NZB/NZW_{F1} mice. *J Exp Med* 129:123 1969

Diagnosis and treatment of a case of recurrent ventricular tachycardia

William H Barry MD

Edwin L Alderman MD

Pat O Daryl MD

Donald C Harrison MD FACC

Stanford Calif

The deficiencies of standard electrocardiographic and clinical criteria in distinguishing ventricular tachycardia from junctional or supraventricular tachycardia with aberrant QRS complexes have recently been emphasized.^{1,2} Because of differences in prognostic implications and in medical and surgical treatments of these conditions this distinction has considerable practical importance. We recently have studied a patient suffering from recurrent refractory tachycardia in whom the techniques of atrial recording, competitive atrial pacing and Holter Recorder monitoring were helpful in establishing a diagnosis of ventricular tachycardia. An accurate diagnosis in this patient permitted subsequent major diagnostic and therapeutic procedures which resulted in control of his arrhythmia.

Case report

R. Z. SCH No 33 30-54 a 6 year old Caucasian man entered Stanford University Hospital for the first time on July 24 1960 because of recurrent tachycardia. The patient had been well until 1959 when he suffered an inferior myocardial infarction.

Following an uneventful recovery he did well until 1961 when he developed paroxysmal tachycardia with aberrant QRS complexes which was terminated by intravenous vasopressors. He was begun on quinidine. Aside from an episode of chest pain diagnosed as pericarditis and treated with a course of steroids in 1962 he did well until July 26 1969 when tachycardia recurred. An electrocardiogram (ECG) taken at that time demonstrated a ventricular rate of 194 per minute and wide aberrant QRS complexes (Fig 1 A). A diagnosis of ventricular tachycardia was made and the patient was cardioverted to normal sinus rhythm (Fig 1 B). On Aug 2 1969 a tachycardia recurred. In comparison with the previous tachycardia the rate was slightly slower at 180 per minute and the QRS complexes had a different configuration (Fig 1 C). This tachycardia was converted to normal sinus rhythm by the administration of intravenous neosynephrine and subsequent arrhythmias were thought to be supra-ventricular tachycardias with aberration. Despite treatment with a variety of antiarrhythmic agents including procainamide propranolol digoxin diphenylhydantoin and quinidine alone and in combinations adequate prevention of this recurrent arrhythmia was not achieved. From August 1969 to July 1970 he had 11 documented episodes of tachycardia. With one exception which was converted with neosynephrine and had an ECG pattern identical to that shown in Fig 1 C all these arrhythmias were resistant to vagal maneuvers required electrical reversal and had the same ECG pattern.

From the Division of Cardiology and Cardiac Surgery, Stanford University School of Medicine, Stanford Calif 94305.
This work was supported in part by the National Institutes of Health Grants N. HE-09058 HE-3399 and HE-00866 and a grant from the American Heart Association. No. 67708.
Received for publication February 15 1971.
Revised manuscript accepted May 11 1971.
From the Division of Cardiology and Cardiac Surgery, Stanford University School of Medicine, Stanford Calif 94305.

Received August 19 1971

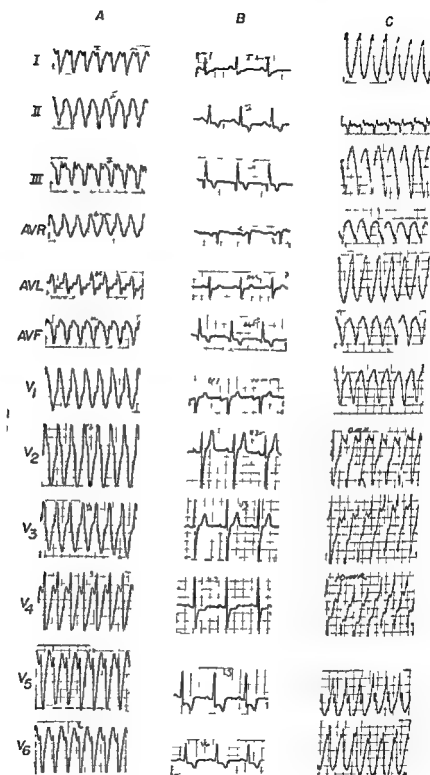
R Z 33 30 54
1970

Fig 1 Standard 12 lead electrocardiographic tracings of the patient during tachycardia (A and C) and during normal sinus rhythm (B). (1) was the most common tachycardia pattern with a rate of 194 per minute and QRS of 0.16 sec. No P waves are discernible. Pattern (C) occurred three times and on two occasions was converted to normal sinus rhythm by intravenous neosynephrine administration. The rate in (C) is 180 per minute. Tracing (B) shows evidence of an old inferior infarction and an intraventricular conduction defect with a QRS of 0.10 sec.

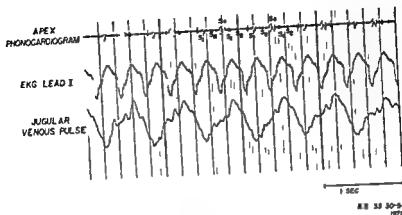


Fig 1 Simultaneous apex phonocardiogram, ECG Lead I and jugular venous pulse tracing. Note the split heart sound and the large A wave and S₁ which appear with every other beat. The first component of S₁ is louder when preceded by atrial contraction.

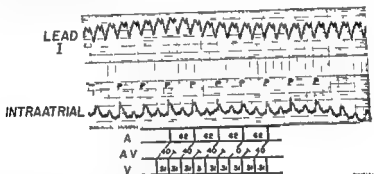


Fig 3 This record shows simultaneous standard ECG Lead I (upper tracing) and unipolar right atrial cavity tracing (lower tracing). P denotes atrial depolarization. Retrograde conduction to the atria is demonstrated with 2:1 block. In the diagram below the lower tracing, P denotes atrial depolarization, A is the atrioventricular conduction, and V is the onset of ventricular depolarization. In the diagram, a ventricular focus is indicated. However, this tracing is also compatible with a junctional pacemaker with retrograde 2:1 block and aberration of the QRS complex (see text).

as shown in Fig 1. The patient tolerated these tachycardias well, with a slight fall in blood pressure and lightheadedness but without symptoms of angina or congestive heart failure. He was referred to Stanford Medical Center because of development of more frequent episodes of tachycardia.

On physical examination the blood pressure was 90/50, pulse 190 to 200 and regular, respirations 16. In the neck, regular jugular venous pulsations at half the heart rate were visible although the venous pressure was normal. The heart size was normal. There was a regular variation of intensity of heart sounds which was difficult to interpret because of the rapid rate. A multilead ECG, jugular venous pulse tracing and apex phonocardiogram taken during the tachyarrhythmia demonstrated a prominent A wave and S occur with every other QRS complex (Fig 2). The ECG on admission was identical to that shown in Fig 1. He failed to respond

to carotid sinus pressure, neosynephrine infusion and edrophonium. He was cardioverted but his tachycardia soon recurred.

In an attempt to establish the mechanism of the tachycardia, the patient was taken to the Cardiac Catheterization Laboratory where under fluoroscopic control an NBII bipolar electrode catheter was introduced into the right atrium. The unipolar right atrial electrogram revealed retrograde 2:1 block with either a ventricular focus or a junctional focus with aberration of the QRS complex (Fig 3). Pacing of the atrium was then attempted with a Medtronic battery-powered unit as described by Fahey and Goldstein⁸ but atrial capture was not possible at the maximum pacemaker rate which was less than that of the tachycardia. A Grass Stimulator with a stimulus isolation unit was then used to pace at a rate of 204 per minute faster than the tachycardia rate of 194 per minute (Fig 4). After three

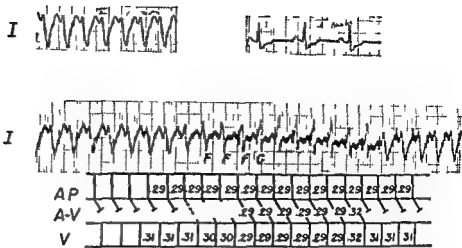


Fig. 1. The upper records show the standard Lead I ECG tracing during tachycardia (left) and sinus rhythm (right). The lower record shows Lead I ECG tracing during tachycardia while atrial pacing was being performed. In the diagram below the record, AP denotes the atrial pacing spike, AV the atrioventricular conduction, and V the onset of ventricular depolarization. F signifies a fusion beat and C the onset of capture which persisted for seven beats. The QRS of the captured beats is similar to that in the same lead during normal sinus rhythm. The P waves are obscured by the QRS complex, and the pacemaker spike R interval is 0.29 sec. The rate during capture is 204 per minute, the basic rate of the tachycardia 194 per minute. Capture ceases when the pacemaker spike R interval prolongs and increased integrade block occurs, allowing emergence of the ventricular tachycardia.

fusion beat, ventricular capture occurred with a prolonged P-R interval (0.29 sec) and a QRS configuration similar to that present in Lead I during normal sinus rhythm. This established a diagnosis of ventricular tachycardia. Conversion to sinus rhythm could not be accomplished by sustained capture followed by gradual lowering of the pacing rate. The patient was then electrically cardioverted and maintained on an intravenous lidocaine infusion.

Subsequently, a Holter Recorder 10-hour monitoring of his ECG revealed numerous short runs of ventricular tachycardia (Fig. 5) usually initiated by a ventricular premature contraction. There was a constant coupling interval between the ventricular premature contraction and the onset of the tachycardia. The tachycardias showed complete A-V dissociation with spontaneous terminations.

While hospitalized, the patient continued to have frequent episodes of ventricular tachycardia and required 14 cardioversions over a five-week period. His treatment included numerous antiarrhythmic medications including the experimental agents bretylium disopyramide and alprenolol and trials of both atrial and ventricular transvenous pacing. Because of failure of medical treatment, coronary angiography and left ventricular angiography were performed to search for a lesion which might be amenable to surgical therapy. He was found to have significant disease of the right and left circumflex coronary arteries and an aneurysm in the posterior wall of the left ventricle. On Aug. 28, 1970, partial excision of the left ventricular scar and a saphenous vein bypass graft to the right coronary artery was accomplished. Evidence of old pericarditis was noted at the time of operation. In the

six months since the operation he has had no further episodes of ventricular tachycardia. Treatment with oral procainamide has been continued because of ventricular premature beats.

Discussion

Classically, the diagnosis of ventricular tachycardia has rested upon the presence of a wide aberrant QRS pattern with independent atrial and ventricular activity. However, it is well established that neither aberration of the QRS complex nor the presence of A-V dissociation unequivocally indicates a ventricular origin of a rhythm.

In a tachycardia with an aberrant QRS complex and nondetectable atrial activity in the standard ECG leads, esophageal or intra-atrial lead records may demonstrate the relationship of atrial and ventricular depolarization.⁴ The diagnosis of an atrial tachycardia can be made with this technique by demonstrating integrade conduction. At rapid atrial rates or with a prolonged PR interval, however, distinguishing between integrade and retrograde conduction can be difficult. His bundle records may prove helpful in this regard.⁵ Retrograde activation of the atria occurs in junctional tachycardia, and the finding of an R-retrograde P interval of 0.10 sec

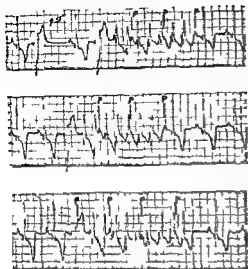


Fig 5 Three Holter Monitor recorded ECG strips demonstrating brief runs of tachycardia with a wide aberrated QRS and a rate of 194 per minute initiated in each case by a ventricular premature beat. There is a constant coupling interval of 0.52 sec. between the ventricular premature beat and the onset of tachycardia. In contrast to the 2:1 retrograde block pattern seen during sustained tachycardia in these spontaneously terminated arrhythmias there is complete AV dissociation. P denotes the P waves.

and or less proves a junctional focus.¹ However junctional tachycardia may occur with retrograde block and complete and incomplete AV dissociation.^{8,9} Moreover ventricular tachycardia is frequently associated with retrograde VA conduction of varying degrees.^{9,10} Therefore when the RP interval is greater than 0.10 second or when there is AV dissociation the origin of a tachycardia may be uncertain.

The presence of aberration does not distinguish a ventricular from a junctional origin. Four types of aberration of supraventricular beats are known to occur:¹ (1) abnormal intraventricular conduction of all conducted supraventricular beats i.e. bundle branch block; (2) conduction through an anomalous pathway i.e. in the Wolff-Parkinson-White syndrome; (3) aberration of junctional escape beats; (4) rate related aberration secondary to incomplete recovery of the conducting system during conduction above a particular rate. There is some question as to the mechanism of aberration which occurs in junctional es-

cape beats.¹¹ It seems likely as described by Kustin¹² that conduction via paraspecific fibers can result in aberration of junctional premature and escape beats. Tachycardias originating in such fibers could conceivably occur and demonstrate fusion and capture phenomena. However the degree of aberration in such beats is not great^{11,12} and the QRS is generally not prolonged to greater than 0.12 second unless a consistent aberration due to incomplete recovery is also present.¹³ Abnormal intraventricular conduction and the Wolff-Parkinson-White syndrome may be detected by examination of the LCG during normal sinus rhythm. A major diagnostic problem therefore lies in determining if a rate related aberration with a junctional focus is the cause of a prolonged abnormal QRS during a recurrent tachycardia.

In the patient described in this report competitive atrial pacing was used to rule out rate related aberration with junctional tachycardia by demonstrating that the conduction system was capable of transmitting impulses without aberration at a rate greater than that of the tachycardia. Because of the marked degree of aberration and prolongation of the QRS in this patient's arrhythmia a junctional tachycardia with aberration due only to conduction via paraspecific fibers¹³ was not considered a reasonable possibility. Thus sustained atrial capture established the diagnosis of ventricular tachycardia in this case. We believe that the usefulness of this technique reported previously in the case described by Lisle and Goldstein² deserves further emphasis. In certain circumstances it may be the only way to eliminate a rate related aberration as a diagnostic possibility in a tachycardia with an abnormal QRS configuration.

Another technique which deserves consideration when approaching problems of this kind is a Holter Recorder monitoring.¹⁴ Frequently the mode of onset of a tachycardia will reveal its mechanism. In the case of a supraventricular tachycardia with a rate related aberration of the QRS for example the arrhythmia may begin with a P wave or the first complex of the tachycardia may not be aberrant.¹ In ventricular tachycardia the arrhythmia may begin with a ventricular premature contraction

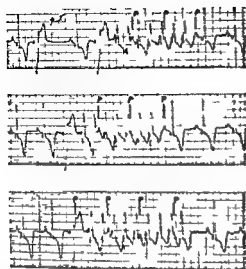


Fig 5 Three Holter Monitor recorded ECG strips demonstrating brief runs of tachycardia with a wide aberrated QRS and a rate of 194 per minute initiated in each case by a ventricular premature beat. There is a constant coupling interval of 0.52 sec. between the ventricular premature beat and the onset of tachycardia. In contrast to the 2:1 retrograde block pattern seen during sustained tachycardia these spontaneously terminated arrhythmias are associated with a complete A-V dissociation. P denotes the P waves.

and or less proves a junctional focus.¹ However junctional tachycardia may occur with retrograde block and complete and incomplete A-V dissociation.^{1,2} Moreover ventricular tachycardia is frequently associated with retrograde V-A conduction of varying degrees.^{3,10} Therefore when the R-P interval is greater than 0.10 second or when there is A-V dissociation the origin of a tachycardia may be uncertain.

The presence of aberration does not distinguish a ventricular from a junctional origin. Four types of aberration of supraventricular beats are known to occur:¹ (1) abnormal intraventricular conduction of all conducted supraventricular beats i.e. bundle branch block (2) conduction through an anomalous pathway i.e. in the Wolff Parkinson White syndrome (3) aberration of junctional escape beats (4) rate related aberration secondary to incomplete recovery of the conducting system during conduction above a particular rate. There is some question as to the mechanism of aberration which occurs in junctional es-

cape beats.^{11,12} It seems likely as described by Austin¹² that conduction via paraspecific fibers can result in aberration of junctional premature and escape beats. Tachycardia originating in such fibers could conceivably occur and demonstrate fusion and capture phenomena. However the degree of aberration in such beats is not great^{11,12} and the QRS is generally not prolonged to greater than 0.12 second unless a coexistent aberration due to incomplete recovery is also present.¹² Abnormal intraventricular conduction and the Wolff Parkinson White syndrome may be detected by examination of the LCG during normal sinus rhythm. A major diagnostic problem therefore lies in determining if a rate related aberration with a junctional focus is the cause of a prolonged abnormal QRS during a recurrent tachycardia.

In the patient described in this report competitive atrial pacing was used to rule out rate related aberration with junctional tachycardia by demonstrating that the conduction system was capable of transmitting impulses without aberration at a rate greater than that of the tachycardia. Because of the marked degree of aberration and prolongation of the QRS in this patient's arrhythmia a junctional tachycardia with aberration due only to conduction via paraspecific fibers¹² was not considered a reasonable possibility. Thus sustained atrial capture established the diagnosis of ventricular tachycardia in this case. We believe that the usefulness of this technique reported previously in the case described by Easley and Goldstein² deserves further emphasis. In certain circumstances it may be the only way to eliminate a rate related aberration as a diagnostic possibility in a tachycardia with an abnormal QRS configuration.

Another technique which deserves consideration when approaching problems of this kind is a Holter Recorder monitoring.¹³ Frequently the mode of onset of a tachycardia will reveal its mechanism. In the case of a supraventricular tachycardia with a rate related aberration of the QRS for example the arrhythmia may begin with a P wave or the first complex of the tachycardia may not be aberrant.⁶ In ventricular tachycardia the arrhythmia may begin with a ventricular premature contraction

in or near the "vulnerable" period of the T wave. The onset of a tachycardia may be very elusive. However, with the Holter Recorder a 10 hour record is obtained, which in this case contained a surprising number of brief runs of tachycardia. The analysis of these tracings was helpful in confirming the diagnosis of ventricular tachycardia. In addition the finding of a constant coupling interval between a ventricular premature contraction and subsequent onset of ventricular tachycardia suggests that a re-entry mechanism was involved in the genesis of the arrhythmia.

The documented history in this case of conversion of tachycardia on two occasions to normal sinus rhythm by administration of nicosynephrine is interesting. The configuration of the QRS on these occasions was somewhat different from that of the patient's usual ventricular tachycardia and the rate slightly slower (Fig. 1, C). It would seem reasonable to assume that these arrhythmias were also ventricular tachycardia in that the conduction system was subsequently shown to be capable of conducting normally at a rate greater than that of the tachycardia. The conversion to sinus rhythm of a tachycardia by a maneuver which increases the vagal tone usually indicates a supraventricular focus. In this case, carotid sinus pressure and edrophonium were ineffective in terminating the arrhythmia. Nicosynephrine may have been effective by virtue of its catecholamine effect on the electrophysiologic properties of the myocardium rather than by increasing vagal tone by its blood pressure elevating effect. Conversion of the tachycardia with a vasopressor initially confused the diagnosis and in another example of the difficulties which may be encountered in distinguishing between ventricular tachycardia and junctional tachycardia with aberration.

Once the diagnosis of ventricular tachycardia was made, failure to achieve control of the arrhythmia by medication and pacing led to a study of the ventricle by means of coronary arteriography and left ventricular angiography. Him¹ has described several mechanisms whereby myocardial ischemia may cause ventricular irritability, and there have been several reports of intractable ventricular tachycardia associated with

left ventricular aneurysm cured by resection of the aneurysm.^{16,17} Therefore both ischemia due to the coronary artery disease and the akinetic area of the ventricular wall were considered possible etiologic factors in the development of the tachycardia, and both coronary bypass surgery and excision of a major portion of the akinetic fibrotic area were performed. The success of the operation in this case may have been due to infarctectomy, coronary artery bypass or infarction of a small portion of the myocardium during operation.

Fortunately tachycardias which cannot be adequately controlled medically are rare. When they are encountered, their mechanism must be accurately defined before major surgery is considered. Atrial recording, competitive atrial pacing, His bundle recordings, and Holter Recorder monitoring can aid the clinician considerably in distinguishing between ventricular tachycardia and supraventricular tachycardia with rate related aberration of the QRS complex.

Summary

A man with a history of remote myocardial infarction developed refractory recurrent tachyarrhythmia with widened QRS complexes. Conversion to sinus rhythm during administration of intravenous vasopressors occurred on several occasions and the arrhythmia was considered to be supraventricular tachycardia with aberration of the QRS. Atrial recording, competitive atrial pacing and Holter monitoring were used to establish a diagnosis of ventricular tachycardia. Subsequent to coronary artery bypass surgery and partial excision of a noncontractile scar from the posterior wall of the left ventricle, he has had no further tachyarrhythmias. The difficulties in differential diagnosis and the techniques used are discussed.

REFERENCES

1. Kassin A D Problems in the differentiation of ventricular arrhythmia from supraventricular arrhythmia with abnormal QRS. *Proc. Cardiovasc. Dis.* 9:1 1966
2. Matsuura R A, Iwaki A A and Kassin A D Reevaluation of electrocardiographic and bedside criteria for diagnosis of ventricular tachycardia. *Circulation* 36:678 1967
3. Casley R M Jr and Goldstein S. Differen

- tation of ventricular tachycardia from junctional tachycardia with aberrant conduction. *Circulation* 33:1015 1968
4. Irons G V Jr, Ginn W M Jr and Orin J E. Contribution of the platinum tipped electrode catheter to the diagnosis of cardiac arrhythmias. *Amer J Cardiol* 21:891 1968
5. Damato A D and Lau S H. Clinical value of the electrogram of the conduction system. *Proc Cardiovasc Dis* 13:119 1960
6. Katz L N and Lick A. Clinical electrocardiography. I. The arrhythmias. Philadelphia 1966. Lea & Febiger Publishers.
7. Blount A W Jr and Kemp V L. Ectopic tachycardias with unusual retrograde conduction to the atria. *Dis Chest* 60:611 1966
8. Lick A and Langendorf R. Recent advances in the differential diagnosis of AV junctional arrhythmias. *AMER HEART J* 6:553 1968
9. Cohn L J, Donoso E and Fredberg C H. Ventricular tachycardia. *Progr Cardiovasc Dis* 9:79 1960
10. Katin A D. Retrograde conduction to the atria in ventricular tachycardia. *Circulation* 40:36 1961
11. Lick A. Aberrant ventricular conduction of escaped beat. *Circulation* 13:107 1956
12. Singer D H, Yeh B K and Hoffman B I. Aberration of supraventricular escape beats. *Circ* 23:158 1961
13. Katin A D. Atrioventricular junctional and escape beats with an altered QRS and fusion. *Circulation* 33:740 1966
14. Corday E, Bazuka V, Tzu Wang, Lan et al. Detection of phantom arrhythmias and evanescent electrocardiographic abnormalities. *JAMA* 193:117 1965
15. Han J. Mechanism of ventricular arrhythmias associated with myocardial infarction. *Amer J Cardiol* 4:800 1969
16. Ritter F R. Intractable ventricular tachycardia due to ventricular aneurysm with surgical cure. *Ann Intern Med* 71:153 1969
17. Cribb O A. Cardiac aneurysm with ventricular tachycardia and subsequent excision of aneurysm. *Circulation* 20:251 1959

Double-outlet right ventricle with left ventricular-right atrial communication Fibrous obstruction of left ventricular outlet by membranous septum and tricuspid leaflet tissue

Andrew J. Megaritz, MD

Richard G. Chambers, MD

A. Louise Calder, MD

Stella Van Praagh, MD

Richard Van Praagh, MD

Fort Worth, Texas and Boston, Mass.

Severe obstruction of the left ventricular outflow tract occurs infrequently with double outlet right ventricle and is of two general types: (1) muscular, and (2) fibrous.

Muscular obstruction is produced by abnormal conal myocardium beneath the great arteries. Such musculature markedly narrows the ventricular septal defect that serves as the only outlet from the left ventricle.^{1,2} Excision of this conal musculature enlarges the ventricular septal defect by raising its "roof," thereby removing the obstruction to the left ventricular outflow tract and permitting successful repair by open heart surgery.^{2,3}

Fibrous obstruction of the left ventricular outflow tract is produced by endocardial cushion tissue of the atrioventricular canal usually by tissue related to the mitral

valve.^{4,5} In the unique case to be presented, obstruction is produced by endocardial cushion tissue related to the tricuspid (not the mitral) valve. Fibrous obstruction of the left ventricular outflow tract associated with double outlet right ventricle has not as yet been corrected surgically.

Case report

This 35 day old white male infant weighed 4.03 kilograms at birth. The mother's pregnancy had been uncomplicated and delivery had been normal. Cyanosis, tachypnea, and splenomegaly were noted immediately after birth. Oxygen (30 per cent) reduced the cyanosis and the patient was digitalized because of cardiomegaly.

Physical examination on admission to the Fort Worth Children's Hospital when he was 15 days old revealed cyanosis of the lips and nailbeds. Weak pulses were present in all extremities and iliac blood pressures (mm Hg) were right arm 110, left arm 100, and right leg 90. Auscultation revealed a nor-

From the Department of Cardiology, Fort Worth Children's Hospital, Anatomical and Clinical Pathology, Hanes Hospital, Fort Worth, Texas, and the Departments of Cardiology and Pathology, Children's Hospital Medical Center, Departments of Pediatrics and Pathology, Harvard Medical School, Boston, Mass.

Supported in part by Grant HL-10436-04 from the National Heart and Lung Institute, National Institutes of Health, Bethesda, Md., and by a grant from the Quebec Medical Research Council, Montreal, Canada.

Received for publication March 26, 1971.

Reprint requests to: Richard Van Praagh, MD, Children's Hospital Medical Center, 300 Longwood Avenue, Boston, Mass. 02115.

Vol. 54
No. 2



Fig 1 Chest roentgenogram showing cardiomegaly (cardiothoracic ratio = 40 per cent), a tilted apex, and somewhat increased pulmonary vascular markings.

mal first heart sound, splitting of the second heart sound, a third heart sound (diastolic gallop) at the lower left sternal border, and Grade 3/6 systolic and diastolic murmurs that were heard best at the apex and left axilla. The lungs were clear to auscultation. The liver was palpated 4 cm. below the right costal margin and the spleen 2 cm. below the left costal margin.

Chest roentgenograms showed progressive cardiomegaly, a globular heart with an up-tilted apex and mildly increased pulmonary vascular markings (Fig 1). Electrocardiography suggested left ventricular hypertrophy and mild atrial enlargement with a somewhat prolonged P-R interval of 0.15 sec. for a rate of 140 per minute (Fig 2). Top normal being 0.11 sec.⁸

Cardiac catheterization when the patient was 23 days of age demonstrated a left-to-right shunt with oxygen step-ups at the right atrial and right ventricular levels (Table I). The catheter entered a patent left superior vena cava into the coronary sinus. The catheter also passed directly from the right atrium into the left ventricle; the left atrium was never entered. The right ventricular pressure was high (90/0-5 mm. Hg) but the left ventricular pressure was 70 mm. Hg higher (160/0-10 mm. Hg). Although neither great artery was entered, the left ventricular pressure was very probably suprasystemic in view of the fluid blood pressures of 90 to 110 mm. Hg noted above.

Selective right ventricular angiocardiography revealed that both great arteries arose from the right ventricle (Fig 3). The left atrium and left ventricle were never visualized. The aortic valve was to the right, posterior and inferior relative to the pulmonary valve (Fig 3b). A curvilinear filling defect beneath the aortic valve suggested subaortic stenosis (Fig 3b). This suggestion was strengthened by the demonstration of moderate tubular hypoplasia of the distal aortic arch (Fig 3b) which was consistent with a low flow aortic arch secondary to subaortic stenosis. A patent ductus arteriosus was not visualized.

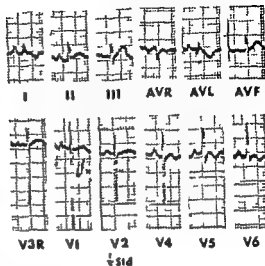


Fig 2 Electrocardiogram suggests left ventricular hypertrophy and right atrial enlargement with mild prolongation of P-R interval (0.15 sec.)

Progressive intractable heart failure led to death at 35 days of age.

At necropsy external inspection of the heart accurately suggested right ventricular hypertrophy and enlargement; the apex being formed largely by the right ventricle (Fig 4a). Enlargement of the main pulmonary artery, mild hypoplasia of the ascending aorta and moderate hypoplasia of the aortic arch were also evident (Fig 4a).

The interior of the right atrium revealed (Fig 4b) marked hypertrophy and enlargement striking hypoplasia of the right superior vena cava which admitted a 1 mm. probe snugly; a prominent Thebesian valve only partly covering a very much enlarged coronary sinus (10 mm. in diameter) which received a persistent left superior vena cava; a fossa ovalis; an anatomically sealed foramen ovale unusual at 35 days of age; and a left ventricular-to-right atrial communication within the superior commissure of the tricuspid valve at the junction of the anterior and septal leaflets measuring 1.5 mm. in diameter and surrounded by thickened firm tricuspid leaflet tissue. This small communication was the only outlet from the left ventricle—indeed the only outlet from the left side of the heart.

The tricuspid valve was enlarged (circumference = 5.5/3.3 cm.) (Fig 4b) and the right ventricle was hypertrophied and enlarged (Figs 4b-d). No ventricular septal defect could be seen from within the right ventricle (Figs 4c-d). At first glance the aortic valve appeared to be separated from the tricuspid valve by a 3 mm. wide band of subaortic conal musculature (Fig 4c). However on closer inspection the anterior leaflet of the tricuspid valve appeared to be in direct fibrous continuity with the left coronary and noncoronary leaflets of the aortic valve—behind this slim band of conal musculature. Such continuity was confirmed by dividing this band of conal muscle (Fig 4d). This band of conal musculature (Fig 4c) was very similar morphologically to the structure designated as the right posterior division of the

Double-outlet right ventricle with left ventricular-right atrial communication: Fibrous obstruction of left ventricular outlet by membranous septum and tricuspid leaflet tissue

Andrew L. Megarity, MD

Richard G. Chambers, MD

A. Louise Calder, MD

Stella Van Praagh, MD

Richard Van Praagh, MD

Fort Worth, Texas, and Boston, Mass

Severe obstruction of the left ventricular outflow tract occurs infrequently with double outlet right ventricle and is of two general types: (1) muscular, and (2) fibrous.

Muscular obstruction is produced by abnormal conal myocardium beneath the great arteries. Such musculature markedly narrows the ventricular septal defect that serves as the only outlet from the left ventricle.^{1,2} Excision of this conal musculature enlarges the ventricular septal defect by raising its "roof," thereby removing the obstruction to the left ventricular outflow tract and permitting successful repair by open heart surgery.³

Fibrous obstruction of the left ventricular outflow tract is produced by endocardial cushion tissue of the atrioventricular canal, usually by tissue related to the mitral

valve.^{4,5} In the unique case to be presented obstruction is produced by endocardial cushion tissue related to the tricuspid (not the mitral) valve. Fibrous obstruction of the left ventricular outflow tract associated with double outlet right ventricle has not as yet been corrected surgically.

Case report

This 35 day old white male infant weighed 4.6 kilograms at birth. The mother's pregnancy had been uncomplicated and delivery had been normal. Cyanosis, tachypnea, and splenomegaly were noted immediately after birth. Oxygen (50 per cent) reduced the cyanosis and the patient was digitalized because of cardiomegaly.

Physical examination on admission to the Fort Worth Children's Hospital when he was 15 days old revealed cyanosis of the lips and nailbeds. Weak pulses were present in all extremities and fluorous blood pressures (mm Hg) were: right arm 110, left arm 100, and right leg 90. Auscultation revealed a not

From the Department of Cardiology, Fort Worth Children's Hospital, Anatomical and Clinical Pathology, Harvard Medical School, Boston, Mass., and the Departments of Cardiology and Pathology, Children's Hospital Medical Center, Departments of Pediatrics and Pathology, Harvard Medical School, Boston, Mass. Supported in part by Grant HE-10436-04 from the National Heart and Lung Institute, National Institutes of Health, Bethesda, Md., and by a grant from the Quebec Medical Research Council, Montreal, Canada. Received for publication March 26, 1971. Reprint requests to: Richard Van Praagh, MD, Children's Hospital Medical Center, 300 Longwood Avenue, Boston, Mass. 02115.



Fig 1 Chest roentgenogram showing cardiomegaly (cardiothoracic ratio = 0 per cent) uptilted apex and somewhat increased pulmonary vascular markings.

mal first heart sound splitting of the second heart sound a third heart sound (diastolic gallop) at the lower left sternal border and Grade 3/6 systolic and diastolic murmurs that were heard best at the apex and left axilla. The lungs were clear to auscultation. The liver was palpated 4 cm. below the right costal margin, and the spleen 2 cm. below the left costal margin.

Chest roentgenograms showed progressive cardiomegaly a globular heart with an uptilted apex and mildly increased pulmonary vascular markings (Fig 1). Electrocardiography suggested left ventricular hypertrophy and right atrial enlargement with a somewhat prolonged P R interval of 0.15 sec. at a rate of 140 per minute (Fig 2) (top normal being 0.11 sec.).

Cardiac catheterization when the patient was 25 days of age demonstrated a left to-right shunt with oxygen step-ups at the right atrial and right ventricular levels (Table 1). The catheter entered a persistent left superior vena cava via the coronary sinus. The catheter also passed directly from the right atrium into the left ventricle; the left atrium was never entered. The right ventricular pressure was 90/0-5 mm. Hg but the left ventricular pressure was 0 mm Hg higher (160/0-10 mm Hg) although neither great artery was entered. The left ventricular pressure was very probably suprasystolic in view of the flush blood pressures of 90 to 110 mm. Hg noted above.

Selective right ventricular angiography revealed that both great arteries arose from the right ventricle (Fig. 3). The left atrium and left ventricle were never visualized. The aortic valve was to the right, posterior and inferior relative to the pulmonary valve (Fig. 3b). A curvilinear filling defect beneath the aortic valve suggested subaortic stenosis. This suggestion was strengthened by the demonstration of moderate tubular hypoplasia of the distal aortic arch (Fig 3b) which is consistent with a low flow aortic arch secondary to subaortic stenosis. A patent ductus arteriosus was not visualized.

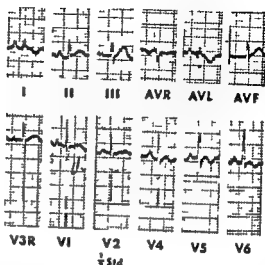


Fig 2 Electrocardiogram suggests left ventricular hypertrophy and right atrial enlargement with mild prolongation of P R interval (0.15 sec.)

Progressive intractable heart failure led to death at 35 days of age.

At necropsy external inspection of the heart accurately suggested right ventricular hypertrophy and enlargement, the apex being formed largely by the right ventricle (Fig 4a). Enlargement of the main pulmonary artery, mild hypoplasia of the ascending aorta and moderate hypoplasia of the aortic arch were also evident (Fig 4a).

The interior of the right atrium revealed (Fig 4b) marked hypertrophy and enlargement striking hypoplasia of the right superior vena cava which admitted a 1 mm. probe snugly; a prominent Thebesian valve only partly covering a very much enlarged coronary sinus (10 mm. in diameter) which received a persistent left superior vena cava a fossa ovalis i.e. an anatomically sealed foramen ovale unusual at 35 days of age and a left ventricular to-right atrial communication within the superior commissure of the tricuspid valve at the junction of the anterior and septal leaflets measuring 1.5 mm. in diameter and surrounded by thickened firm tricuspid leaflet tissue. This small communication was the only outlet from the left ventricle—indeed the only outlet from the left side of the heart.

The tricuspid valve was enlarged (circumference = 5.5/3 cm.) (Fig 4b) and the right ventricle was hypertrophied and enlarged (Figs. 4b-d). No ventricular septal defect could be seen from within the right ventricle (Figs 4c-d). At first glance the aortic valve appeared to be separated from the tricuspid valve by a 3 mm. wide band of subaortic conal musculature (Fig 4c). However on closer inspection the anterior leaflet of the tricuspid valve appeared to be in direct fibrous continuity with the left coronary and noncoronary leaflets of the aortic valve—behind this slim band of conal musculature. Such continuity was confirmed by dividing this band of conal muscle (Fig 4d). This band of conal musculature (Fig 4c) was very similar morphologically to the structure designated as the right posterior division of the

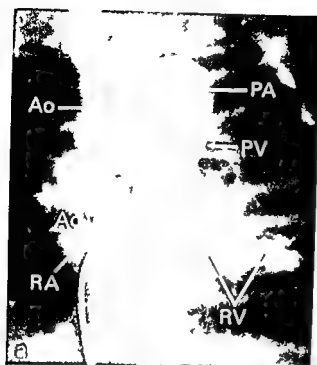


Fig. 3a Selective right ventricular angiogram in posterior-anterior projection. Aorta (Ao) and pulmonary artery (PA) both are above morphologically right ventricle (RV). Pulmonary valve (PV) is anterior superior and to the left of aortic valve (Ao). PA is dilated. RA = right atrium.

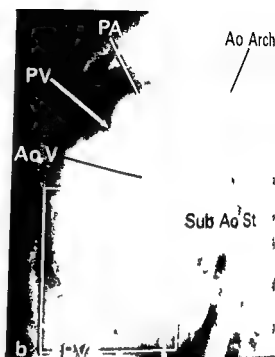


Fig. 3b Selective right ventricular angiogram in anterior projection. A curvilinear filling defect is seen beneath aortic valve (AoV) accurately suggesting subaortic stenosis (Sub Ao St). Tricuspid aortic arch (Ao Arch) displays tubular hypoplasia. PA = pulmonary artery. PV = pulmonary valve. RV = right ventricle.

Table 1 Cardiac catheterization findings

Site	O ₂ saturation (%)	Pressure (mm Hg)
Left superior ventricle	52	
Right atrium	57	$\lambda = 7 \text{ v} = 4$
Right ventricle	78	90/0-5
Left ventricle	98	160/0-10
Right ventricle → Right atrium → Left ventricle		80/0-8 → $\lambda = 10 \rightarrow 160/0-10$

septal band in a previous study of truncus arteriosus communis (see Fig. 4a and c of that paper).¹⁰

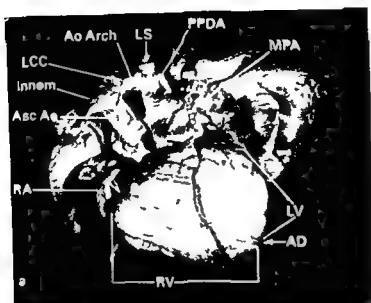
Why is this structure not a hypoplastic parietal band (crista supraventricularis)? It looks quite like it—running from the ventricular septum to the parietal (free) wall above the pars membranacea septi and the anterior leaflet of the tricuspid valve (Figs. 4c, d). This conal musculature could certainly be regarded as a parietal band in the sense that it runs to the parietal wall. However, this structure may well not represent the parietal band because the structure so designated also forms the conal septum dividing the aortic and pulmonary outflow tracts. In this heart there was no conal septum dividing the aortic and pulmonary outflow tracts inasmuch as there was no grossly recognizable myocardium beneath the aortopulmonary septum, the semilunar valves being in direct fibrous continuity with each other (Fig. 4c). Hence the parietal band (crista supra-

ventricularis) appeared to be absent at least anteriorly.

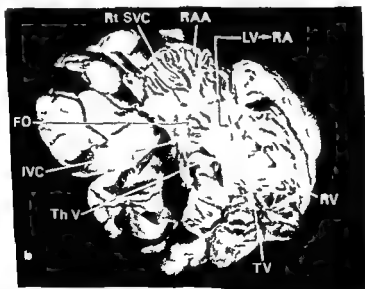
However, this band of conal musculature could represent the inferior (caudal) end of the true parietal band if a large conal septal defect were present superiorly beneath the aortopulmonary septum (Fig. 4c).

This band of conal myocardium is not regarded as subaortic conal free wall (as distinct from conal septal) musculature because division of this band demonstrated aortic tricuspid fibrous continuity behind it (Fig. 4d).

This conal band was visualized angiographically (Fig. 3b). It appeared to produce a most uncommon type of muscular subaortic stenosis, leading to hypoplasia of the aortic arch probably because of reduced aortic blood flow. Had this band of conal muscle not been located where it was (Figs. 4c, d), the high ventricular septal defect usually



Figs. 4a through 4f Autopsy specimen of heart and lungs. a External frontal view accurately suggests hypertrophy and enlargement of right ventricle (RV) Note that RV forms cardiac apex. This in turn gives a sigmoid contour to anterior descending coronary artery (AD) More than the usual amount of left ventricle (LV) is seen from the front accurately suggesting left ventricular hypertrophy and enlargement. Right atrium (RA) appears hypertrophied and enlarged but left atrium is not seen from the front. Relation between great arteries appears to be normal Main pulmonary artery (MPA) is dilated Ascending aorta (Asc Aa) is mildly hypoplastic hypoplasia of transverse aortic arch (Ao Arch) becoming moderately marked distal to innominate artery (Innom) Functionally closed but probe patent ductus arteriosus (PPDA) is seen LCC = left common carotid artery LS = left subclavian artery Photography in Figs. 4a through 4f was by Pauline McRae Maniee Calendo and Terence Wrighton lettering was by Donna Larina



Figs. 4b Opened right atrium tricuspid valve (TV) and right ventricular inflow tract (RV) Note the hypertrophy and enlargement of the right atrial appendage (RAA) and RV marked hypoplasia of ostium of right superior vena cava (Rt SVC) sealed foramen ovale or fossa ovalis (FO) prominent Thebesian valve (Th V) partly covering the markedly enlarged ostium of coronary sinus that receives a persistent left superior vena cava enlarged tricuspid valve (TV) small LV RA communication opening into superior commissure of TV and serving as sole outlet from left side of heart.

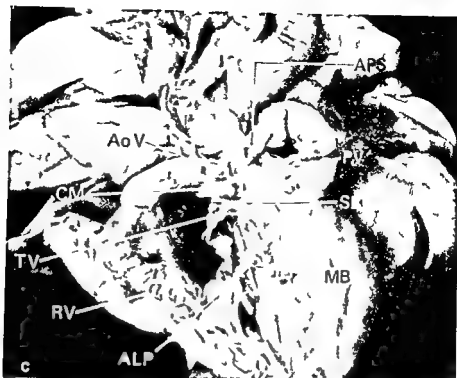


Fig. 4c Right ventricular outflow tract. Both great arteries arise from RV. There is no parietal band or conal septum beneath aorticopulmonary septum (APS). Hence aortic valve (AoV) and pulmonary valve (PV) are in fibrous continuity. Beneath AoV there is a 3 mm wide band of conal musculature (CM) running from ventricular septum to RV free wall above anterior leaflet of tricuspid valve (TV). CM probably produced subaortic stenosis (Fig. 3b). CM is very similar morphologically to right posterior division of septal band (SB) but could represent an inferior remnant of parietal band (conal septum or crista supraventricularis). AoV-TV fibrous continuity appeared to be present behind (dorsal to) CM. ALP = anterolateral papillary muscle. MB = moderator band.

associated with double outlet right ventricle very probably would have been present in this case. Hence although it is accurate to describe the severe obstruction of the left ventricular outflow tract in this case as fibrous (produced by pars membranacea septi and by the anterior and septal leaflets of the tricuspid valve) this conal band (Fig. 4c) also appears to have played an essential if secondary role by reducing the size of the interventricular foramen sufficiently for it to be obstructed by atrioventricular endocardial cushion tissue.

Despite the apparent subaortic stenosis produced by this band of conal myocardium, the aortic valve was tricuspid and of normal size (circumference = 2.3/2.2 cm) (Fig. 4c). The pulmonary valve was tricuspid and enlarged (circumference = 3.3/2.6 cm) (Fig. 4c). The subpulmonary conus was not under developed in the sense that the minimum distance between the pulmonary valve and the tricuspid valve was normal (7/6 mm). The coronary ostia and distributions were normal. The ductus arteriosus was functionally closed but probe patent (Fig. 4a). Hypoplasia of the aortic arch was moderate (circumference = 0.9/1.2 cm) (Figs. 3b and 4a).

The left atrium (Fig. 4e) was hypertrophied but not enlarged. The mitral annulus was somewhat smaller than normal (1.9/2.5 cm) but congenital mitral stenosis did not appear to be present there being no obliteration of interchordal spaces or reduction of interpapillary muscle distance (Fig. 4e). However the papillary muscles were hypoplastic (Fig. 4e).

The left ventricle (Fig. 4f) was hypertrophied and enlarged. The fibrous obstruction of the left ventricular outflow tract could be seen with some difficulty from the left ventricular aspect (Fig. 4f) but was readily apparent from the right atrium (Fig. 4b) the only outlet from the left side of the heart being a small left ventricular to-right atrial communication.

Discussion

This is the first reported case of a remarkable anomaly: double outlet right ventricle in which the only outlet from the left side of the heart is a small left ventricular to-right atrial communication. Severe obstruction of the left ventricular outflow tract was produced by atrioventricular endocardial cushion tissue that was intimately related to the tricuspid valve (Fig. 4b). In this regard it should be recalled that the pars membranacea septi is formed by atrioventricular endocardial cushion tissue intimately related to the tricuspid valve (the right tubercles)^{11,12} and that a left ventricular to right atrial communication is a defect in the atrioventricular portion of the pars membranacea septi.¹¹ Hence it is probable though it may seem, it is only a

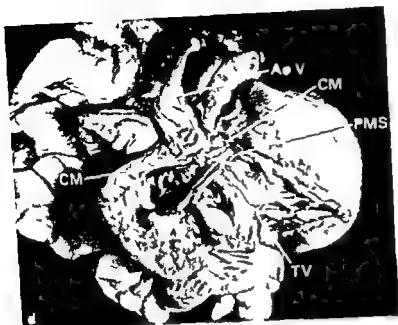


Fig 4d Dissection of CM proved Ao & TV fibrous continuity. Note that no ventricular septal defect is visible within RV. The L & R defect is within fibrous membranous septum (PMS). See also Fig 4b.

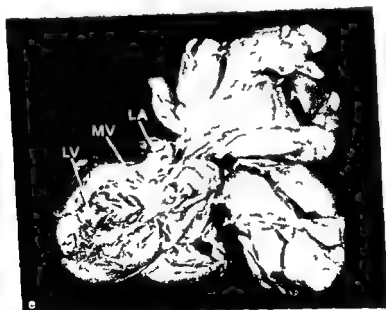


Fig 4e Opened left atrium (LA), mitral valve (MV) and left ventricle (LV). LA is hypertrophied but not enlarged. MV is mildly hypoplastic as are associated papillary muscles. LV is otherwise hypertrophied and enlarged.

slight oversimplification to state that in this case severe stenosis of the left ventricular outflow tract was produced by tricuspid valvular tissue (Fig 4b).

Nor is this case entirely without precedent. Obstruction of the left ventricular

outflow tract due to atrioventricular endocardial cushion tissue related to the mitral valve has been reported.^{1,2} Tricuspid valvular tissue also has infrequently been documented as a cause of obstruction of the left ventricular outflow tract^{3,4} but not in

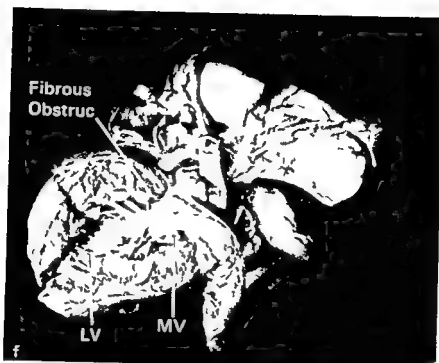


Fig 4f LV outflow tract leading to fibrous obstruction (*Fibrous Obstruc*)

association with double outlet right ventricle.

It has been previously suggested² that obstruction of the left ventricular outflow tract be incorporated into classifications of double outlet right ventricle. It is now known that such obstruction can be either muscular^{1,2} or fibrous (this case). The muscular type of obstruction is amenable to correction by open heart surgery.^{2,3} The fibrous type has not been repaired surgically to date. The anatomic findings in the present case seem to suggest that surgical correction would be difficult or impossible. The interventricular portion of the pars membranacea septum is so small (5 by 2 mm) that even complete removal of the membranous part of the ventricular septum probably would not eliminate the obstruction to the left ventricular outflow tract. Thus on the basis of the very limited data available, it seems probable that the muscular type of obstruction can be corrected surgically but that the fibrous type of obstruction may prove to be inoperable by present methods.

Will it be possible to make the differential diagnosis between the operable muscular type of obstruction and the probably inoperable fibrous type? Data are presently far too limited to permit a definite answer to this question. However, high quality

angiocardiography might well make it possible to recognize the presence of a muscular subaortic conus with a somewhat higher and more anterior aortic valve in the muscular type,² as opposed to the absence of a subaortic conus with a relatively lower and more posterior aortic valve in the fibrous type (Fig 3).

There is a widespread view that double outlet right ventricle is characterized by semilunar valves that are approximately side by side and at about the same height,^{17,18} associated with a bilateral conus (persistent bulboventricular flange).¹⁹ The present case is an exception to all of the foregoing generalizations. This case demonstrates that it is possible to have double outlet right ventricle with a unilateral (subpulmonary) conus. Absence of subaortic conal musculature is indicated by the presence of aortic tricuspid fibrous continuity (Fig 4d). A bilateral conus (persistent bulboventricular flange) is not essential to the morphogenesis of double outlet right ventricle. For reasons that remain unclear, the membranous septum formed beneath the *left* side of the aortic valve in this case, instead of beneath the right side as occurs normally.

Summary

Double outlet right ventricle can be

sociated with obstruction of the left ventricular outflow tract of two types—muscular and fibrous. The muscular form can be corrected by open heart surgery, but the fibrous type may prove to be inoperable by present methods. The angiographic differential diagnosis of muscular and fibrous obstructions is considered briefly.

A unique case of fibrous obstruction of the left ventricular outflow tract associated with double-outlet right ventricle was presented in a 35-day old white male infant. The only outlet from the left side of the heart was a small left ventricular to right atrial communication. This is the first reported case of atrioventricular endocardial cushion tissue closely related to the tricuspid valve producing fibrous obstruction of the left ventricular outflow tract in association with double-outlet right ventricle.

This case also illustrates that it is possible for double outlet right ventricle to occur with aortic atrioventricular fibrous continuity. A bilateral conus—persistence of the bulboventricular flange—is not a constant finding in double-outlet right ventricle.

We wish to thank Marty Holmes for assistance in preparation of the manuscript.

REFERENCES

- 1 Serrato M, Arevalo F, Goldman E, J Hastreiter A and Miller R. A Obstructive ventricular septal defect in double outlet right ventricle. *Am J Cardiol* 19:457 1967
- 2 Lavoie R, Sestier F, Gilbert G, Chamedes L, Van Praagh R and Grondin P. Double outlet right ventricle with left ventricular outflow tract obstruction due to small ventricular septal defect. *Am HEART J* 82:290 1971
- 3 Mason D T, Morrow A G, Elkins R C and Friedman W. Origin of both great vessels from the right ventricle associated with severe obstruction to left ventricular outflow. *Am J Cardiol* 24:118 1969
- 4 Terence C. Atrio-ventricular defect of membranous septum. Left ventricular right atrial communication with malformed mitral valve simulating aortic stenosis. Report of a case. *Bull Johns Hopkins Hosp* 100:209 1957
- 5 Lauer R M, DuShane J W and Edwards J E. Obstruction of the left ventricular outlet in association with ventricular septal defect. *Circulation* 24:110 1960
- 6 Sellers R D, Lillehei C W and Edwards J E. Subaortic stenosis caused by anomalies of the atrioventricular valves. *J Thoracic & Cardiovas Surg* 48:289 1964
- 7 Jue K I and Edwards J E. Anomalous attachment of mitral valve causing subaortic stenosis. Observations in a case with other cardiac anomalies and multiple spleens. *Circulation* 34:978 1967
- 8 Van Praagh R, Corwin R B, Dahlquist E H, Freedom R M, Mattioli L and Nebenzar R A. Tetralogy of Fallot with severe left ventricular outflow tract obstruction due to anomalous attachment of the mitral valve to the ventricular septum. *Am J Cardiol* 26:73 1970
- 9 Guntheroth W G. Pediatric electrocardiography. Normal and abnormal patterns incorporating the vector approach. Philadelphia 1965 W B Saunders Co p 73
- 10 Van Praagh R and Van Praagh S. The anatomy of common aorticopulmonary trunk (truncus arteriosus communis) and its embryologic implications. A study of 57 necropsy cases. *Am J Cardiol* 16:406 1963
- 11 Takahashi S. Notes on the formation of the cardiac septa in the chick. *J Anat (London)* 81:168 1923
- 12 Odgers I N B. The development of the paramembranous septa in the human heart. *J Anat (London)* 72:247 1938
- 13 Goor D A, Lillehei C W, Rees R and Edwards J E. Isolated ventricular septal defect. Developmental basis for various types and presentation of classification. *Chest* 38:468 1970
- 14 Sellers R D, Lillehei C W and Edwards J E. Subaortic stenosis caused by anomalies of the atrioventricular valves. *J Thoracic & Cardiovas Surg* 48:289 1964
- 15 Layman T E and Edwards J E. Anomalies of the cardiac valves associated with complete transposition of the great vessels. *Am J Cardiol* 19:247 1967
- 16 Riemschneider T A, Goldberg S J, Ruttenberg H G and Gyepes M T. Subpulmonic obstruction in complete (d) transposition produced by redundant tricuspid tissue. *Circulation* 39:603 1969
- 17 Neufeld H N, DuShane J W and Edwards J E. Origin of both great vessels from the right ventricle. I. Without pulmonary stenosis. *Circulation* 23:399 1961
- 18 Neufeld H N, DuShane J W and Edwards J E. Origin of both great vessels from the right ventricle. II. With pulmonary stenosis. *Circulation* 23:603 1961
- 19 Van Mierop L H S and Wiglesworth F W. Pathogenesis of transposition complexes. II. Anomalies due to faulty transfer of the posterior great artery. *Am J Cardiol* 12:776 1963

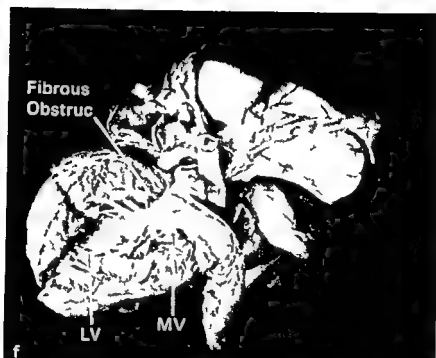


Fig 4f LV outflow tract leading to fibrous obstruction (*Fibrous Obstruc*)

association with double outlet right ventricle.

It has been previously suggested² that obstruction of the left ventricular outflow tract be incorporated into classifications of double outlet right ventricle. It is now known that such obstruction can be either muscular^{1,2} or fibrous (this case). The muscular type of obstruction is amenable to correction by open heart surgery.^{2,3} The fibrous type has not been repaired surgically to date. The anatomic findings in the present case seem to suggest that surgical correction would be difficult or impossible. The interventricular portion of the perimembranous septum is so small (5 by 2 mm) that even complete removal of the membranous part of the ventricular septum probably would not eliminate the obstruction to the left ventricular outflow tract. Thus, on the basis of the very limited data available, it seems probable that the muscular type of obstruction can be corrected surgically, but that the fibrous type of obstruction may prove to be inoperable by present methods.

Will it be possible to make the differential diagnosis between the operable muscular type of obstruction and the probably inoperable fibrous type? Data are presently far too limited to permit a definite answer to this question. However, high quality

angiocardiography might well make it possible to recognize the presence of a muscular subaortic conus with a somewhat higher and more anterior aortic valve in the muscular type,² as opposed to the absence of a subaortic conus with a relatively lower and more posterior aortic valve in the fibrous type (Fig 3).

There is a widespread view that double outlet right ventricle is characterized by semilunar valves that are approximately side by side and at about the same height^{17,18} associated with a bilateral conus (persistent bulboventricular flange).¹⁹ The present case is an exception to all of the foregoing generalizations. This case demonstrates that it is possible to have double-outlet right ventricle with a unilateral (subpulmonary) conus. Absence of subaortic conal musculature is indicated by the presence of aortic tricuspid fibrous continuity (Fig 4d). A bilateral conus (persistent bulboventricular flange) is not essential to the morphogenesis of double outlet right ventricle. For reasons that remain unclear, the membranous septum formed beneath the left side of the aortic valve in this case, instead of beneath the right side as occurs normally.

Summary

Double outlet right ventricle can be



Fig 1 Roentgenograms of an upper (A) and a lower (B) extremity show extensive calcification that outlines the entire arterial tree. Note lack of osteodystrophy.



Fig 2 Section of radial artery demonstrates calcific infiltration of the media (arrow) and edematous intimal thickening. (Hematoxylin and eosin, X20)

Azotemic arteriopathy

Herman Rosen, MD, IACP*

Sandor A. Friedman MD**

Albert L. Ratzner, MD***

Kurt Gerstmann MD****

Brooklyn, NY

The metastatic calcification seen in chronic renal failure often involves the peripheral arteries. This vascular calcification is not always innocent and may lead to significant arterial insufficiency.^{1,2} We recently had the opportunity to observe a uremic patient with widespread arterial calcification and ischemia of several organs. Careful examination of his vessels at necropsy revealed an unusual lesion which may possibly be related to azotemia.

Case report

S.S., a 60-year-old Caucasian man, entered the Coney Island Hospital because of progressive dyspnea on exertion and leg edema for six months. He was known to have had moderate hypertension for 20 years and mild diabetes mellitus controlled by diet. Three years prior to hospitalization anemia and a blood urea nitrogen (BUN) of 26 mg per 100 ml were discovered. There was no history of exposure to nephrotoxins, ingestion of vitamin D, dysuria or hematuria.

Physical examination revealed a pale, orthopneic, lethargic man with asterixis. The blood pressure was 160/85 mm Hg and the pulse rate was 82 per

minute. The neck veins were distended and rales were present at both lung bases. Cardiac examination revealed a heaving apical impulse in the sixth intercostal space at the anterior axillary line and a protodiastolic gallop. A smooth, tender liver was palpable 6 cm below the right costal margin. There was pitting edema of the feet and ankles. Femoral popliteal dorsalis pedis and radial pulses were palpable bilaterally, but the posterior tibial pulses were absent.

The hematocrit was 31 per cent and the white blood cell count was 6,900 per cubic millimeter with a normal differential. The BUN was 74 mg per 100 ml, the serum creatinine was 7.4 mg per 100 ml, and the fasting blood sugar was 163 mg per 100 ml. Twenty-four hour urine collections revealed an endogenous creatinine clearance of 5 to 6 ml per minute and protein excretion of 2.5 Gm per 24 hours. The serum calcium was 8.2 to 10.6 mg per 100 ml and the phosphorus was 6.9 to 8.3 mg per 100 ml. The serum albumin was 2.3 Gm per 100 ml and the globulin was 3.6 Gm per 100 ml. The alkaline phosphatase was 4.3 to 5.3 Bessie Lowry units. A chest roentgenogram showed cardiomegaly. Nephrotomograms revealed contracted kidneys. X-rays of the hands failed to demonstrate subperiosteal bone resorption but did show calcification of the digital arteries.

The patient was treated with digoxin and furose

From the Departments of Medicine and Pathology, Coney Island Hospital affiliated with the Medical College of Brooklyn, N.Y.

Received for publication March 31, 1971.

Reprint requests to: Herman Rosen, MD, Chief, Nephrology Division, Coney Island Hospital, Ocean Avenue Parkway, Brooklyn, N.Y. 11235.

*Chief, Nephrology Division, Coney Island Hospital, Brooklyn, N.Y.

**Chief, Internal Medicine Division, Coney Island Hospital, Brooklyn, N.Y.

***Fellow, Nephrology Division, Coney Island Hospital, Brooklyn, N.Y.

****Chief, Pathology Services, Coney Island Hospital, Brooklyn, N.Y.



Fig. 7 Section of small branch of middle cerebral artery in corpus callosum demonstrates massive calcific replacement of the media sparing of the intima and severe reduction in luminal caliber (Hematoxylin and eosin X128)

Fig. 8 Microscopic examination revealed chief cell hyperplasia with groups showing eosinophilic transformation of the cytoplasm. No fat cells were seen. Multiple sections of bone were grossly and microscopically normal. No evidence of increased resorption was seen.

Discussion

Arterial calcification even without other evidence of metastatic deposits is not uncommon in patients with chronic renal failure.^{1,2,7} Although the arterial involvement can be clearly visualized by plain roentgenography, there usually is no obvious clinically significant vascular impairment. However, several patients have been described with serious problems attributable to this calcific process. Mallick and Berlyne⁸ described three uremic patients taking vitamin D who developed massive calcium deposition that prevented insertion of shunts for hemodialysis. In addition, there have been three reports of calcific arterial occlusion and digital gangrene in uremic patients.^{9,10}

The present case of widespread arterial calcification and gangrene of the upper and lower extremities in association with uremia is the first to be reported with complete histology which seems to point to the reason

for the arterial insufficiency. Arterial pathology and obstruction of an extraordinary nature and extent was found not only in the vessels of the extremities but also in the blood supply of the brain and entire gastrointestinal tract. The histologic appearance of the arteries demonstrated marked luminal compression due mainly to heavy calcific infiltration of the media and partially to reactive connective tissue swelling and hyperplasia of the intima (see Figs. 2 to 4). This pathology is clearly different from arteriosclerosis obliterans seen in patients with diabetes mellitus where arterial obstruction is associated with atheromatous replacement of the intima.

Although medial calcification also occurs in medium-sized arteries in many non-uremic individuals (Monckeberg sclerosis), in such instances it does not result in arterial obstruction. A vasculitis or collagen disease is excluded as the cause of arterial insufficiency in our patient by the absence of thrombosis and inflammatory reaction.

The pathogenesis of arterial calcification in uremia is not well understood but must be related to altered calcium metabolism. Renal failure results in acidosis, increased



Fig 3 Section of submucosal branch of the gastric artery shows marked medial calcification (Hematoxylin and eosin $\times 32$)

mide responded with subjective improvement and loss of peripheral edema and was discharged from the hospital. During the next six months he developed progressive edema in spite of increasing doses of furosemide up to 1.5 Gm daily; he became increasingly lethargic, disoriented, and anorectic and required rehospitalization. The blood pressure was 100/70 mm Hg. Again the neck veins were markedly distended and bibasilar rales were present. A pleural friction rub was audible over the left lateral lung fields but cardiac findings were unchanged. Anasarca with ascites and edema to the hips was present. The subclavian axillary, femoral, popliteal, dorsalis pedis and right brachial pulses were of normal intensity. The right radial pulse was diminished; the left brachial and radial and both posterior tibial pulses were absent. The arteries had a rocklike consistency with nodular irregularities. The fingers of both hands were cold and cyanotic and there was mottling and ecchymosis of the second, third, and fourth fingers of the left hand. The right heel was frankly gangrenous.

Results of blood chemistry tests were essentially unchanged except for the BUN, which had risen to 182 mg per 100 and the serum creatinine, which was now 9.4 mg per 100 ml. X-rays of all extremities (Fig 1) revealed extensive calcification of large and small arteries including the digital arteries of the hands and feet and outlining the entire arterial tree. Abdominal films showed calcification of the mesenteric and iliac vessels. Peritoneal dialysis was performed with good exchanges and reduction of serum creatinine to 4.1 mg per 100 ml, but the patient's mental status did not improve. During the next 12 days extensive gangrene of the fingers of both hands and the glans penis developed. His condition progressively deteriorated and he died.

Postmortem examination. Necropsy revealed extensive dry gangrene of the second, third, fourth, and fifth digits of the right hand, the second, third, and fourth digits of the left hand, the right heel, and the penis.

Patchy but massive calcification of the media was found in all the peripheral arteries from the iliac and subclavian to the digital vessels (Fig 2), celiac and mesenteric arteries, submucosal vessels of the entire gastrointestinal tract (Fig 3), and cerebral vessels, particularly the middle cerebral arteries and their branches (Fig 4). The lumina of these vessels were compressed and reduced to about one third of their normal caliber in many areas. The intima was thickened in some areas by loose edematous connective tissue but was relatively free of atheromatous degeneration (Fig 2). On the other hand, there was extensive partially calcified intimal atheromatosis of the renal and coronary arteries.

The heart weighed 550 grams with gross dilatation and hypertrophy of both ventricles. Numerous foci of fibrosis and calcification were present in the left ventricular myocardium and interventricular septum. Examination of the lungs revealed calcium deposits in many alveolar septa and subpleural zones.

The kidneys were atrophic, weighing 180 grams together, and demonstrated marked nephrosclerosis. There were numerous areas of focal fibrosis and calcific deposits in the cells and lumina of the tubules (Fig 5) as well as the glomeruli.

The rectal mucosa was sloughed and necrotic but the remainder of the gastrointestinal tract was intact. Liver, gallbladder, and spleen were normal. Ictal bilrois of the ileitis was found in the pancreas.

All four parathyroid glands were uniformly enlarged to three to five times normal; the largest

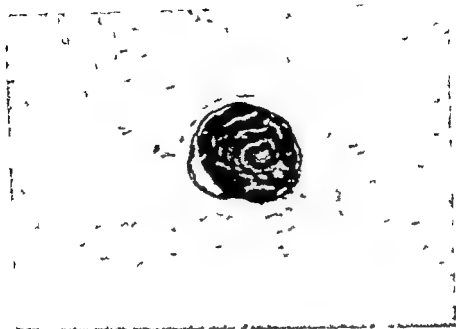


Fig. 4. Section of small branch of middle cerebral artery in corpus callosum demonstrates massive calcific replacement of the media, parietal layer of the intima and severe reduction in luminal caliber (Hematoxylin and eosin $\times 128$).

weighing 2 grams. Microscopic examination revealed chief cell hyperplasia with groups showing eosinophilic transformation of the cytoplasm. No fat cells were seen. Multiple sections of bone were grossly and microscopically normal. No evidence of increased resorption was seen.

Discussion

Arterial calcification even without other evidence of metastatic deposits is not uncommon in patients with chronic renal failure.^{1,2,7} Although the arterial involvement can be clearly visualized by plain roentgenography, there usually is no obvious clinically significant vascular impairment. However, several patients have been described with serious problems attributable to this calcific process. Mallick and Berlyne² described three uremic patients taking vitamin D who developed massive calcium deposition that prevented insertion of shunts for hemodialysis. In addition, there have been three reports of calcific arterial occlusion and digital gangrene in uremic patients.^{2,8}

The present case of widespread arterial calcification and gangrene of the upper and lower extremities in association with uremia is the first to be reported with complete histology which seems to point to the reason

for the arterial insufficiency. Arterial pathology and obstruction of an extraordinary nature and extent was found not only in the vessels of the extremities but also in the blood supply of the brain and entire gastrointestinal tract. The histologic appearance of the arteries demonstrated marked luminal compression due mainly to heavy calcific infiltration of the media and partially to reactive connective tissue swelling and hyperplasia of the intima (see Figs. 2 to 4). This pathology is clearly different from arteriosclerosis obliterans seen in patients with diabetes mellitus where arterial obstruction is associated with atheromatous replacement of the intima.

Although medial calcification also occurs in medium sized arteries in many non-uremic individuals (Monckeberg sclerosis) in such instances it does not result in arterial obstruction. A vasculitis or collagen disease is excluded as the cause of arterial insufficiency in our patient by the absence of thrombosis and inflammatory reaction.

The pathogenesis of arterial calcification in uremia is not well understood but must be related to altered calcium metabolism. Renal failure results in acidosis, increased



Fig. 3 Section of submucosal branch of the gastric artery shows marked medial calcification (Hematoxylin and eosin $\times 32$)

mude responded with subjective improvement and loss of peripheral edema and was discharged from the hospital. During the next six months he developed progressive edema in spite of increasing doses of furosemide up to 1.5 Gm daily; he became increasingly lethargic, disoriented, and anorectic and required rehospitalization. The blood pressure was 100/70 mm Hg. Again the neck veins were markedly distended and bibasilar rales were present. A pleural friction rub was audible over the left lateral lung fields but cardiac findings were unchanged. Anasarca with ascites and edema to the hips was present. The subclavian axillary femoral popliteal dorsalis pedis and right brachial pulses were of normal intensity. The right radial pulse was diminished, the left brachial and radial and both posterior tibial pulses were absent. The arteries had a rocklike consistency with nodular irregularities. The fingers of both hands were cold and cyanotic and there was mottling and ecchymosis of the second, third, and fourth fingers of the left hand. The right heel was frankly gangrenous.

Results of blood chemistry tests were essentially unchanged except for the BUN which had risen to 182 mg per 100 ml and the serum creatinine which was now 9.4 mg per 100 ml. X rays of all extremities (Fig. 1) revealed extensive calcification of large and small arteries including the digital arteries of the hands and feet and outlining the entire arterial tree. Abdominal films showed calcification of the mesenteric and iliac vessels. Peritoneal dialysis was performed with good exchange and reduction of serum creatinine to 4.1 mg per 100 ml but the patient's mental status did not improve. During the next 12 days extensive gangrene of the fingers of both hands and the glans penis developed. His condition progressively deteriorated and he died.

Postmortem examination. Necropsy revealed extensive dry gangrene of the second, third, fourth, and fifth digits of the right hand, the second, third, and fourth digits of the left hand, the right heel, and the penis.

Itchy but massive calcification of the media was found in all the peripheral arteries from the iliac and subclavian to the digital vessels (Fig. 2), aortic and mesenteric arteries, submucosal vessel of the entire gastrointestinal tract (Fig. 3), and cerebral vessels, particularly the middle cerebral arteries and their branches (Fig. 4). The lumina of these vessels were compressed and reduced to about one third of their normal caliber in many areas. The intima was thickened in some areas by loose edematous connective tissue but was relatively free of atheromatous degeneration (Fig. 2). On the other hand, there was extensive partially calcified intimal atheromatosis of the renal and coronary arteries.

The heart weighed 550 grams with gross dilatation and hypertrophy of both ventricles. Numerous foci of fibrosis and calcification were present in the left ventricular myocardium and interventricular septum. Examination of the lungs revealed calcium deposits in many alveolar septa and subpleural zones.

The kidneys were atrophic, weighing 180 grams together and demonstrated marked nephroclerosis. There were numerous areas of focal fibrosis and calcific deposits in the cells and lumina of the tubules (Fig. 5) as well as the glomeruli.

The rectal mucosa was sloughed and necrotic but the remainder of the gastrointestinal tract was intact. Liver, gallbladder, and spleen were normal. Lateral fibrosis of the pancreas was found in the pancreas.

All four parathyroid glands were uniformly enlarged to three to five times normal; the largest

tragic event—the development of gangrene—occurred. In retrospect the impairment of sensorium was out of proportion to the degree of uremia and did not improve preterminally despite adequate peritoneal dialysis. Local ischemia may have been partially responsible. The necrotic bowel found at necropsy was probably related to arterial insufficiency and cardiac failure.

It is tempting to speculate that progressive calcific circulatory insufficiency leading to malfunction of vital organs goes undetected in some uremic patients. Indeed the kidney dysfunction itself may be aggravated by a decreasing renal blood flow in some cases. More data are needed to test the validity of this speculation. Patients with chronic renal insufficiency should be followed with x-rays taken with the proper technique for demonstrating vascular calcification and close attention should be given to the peripheral pulses. Autopsies should include careful examination of the entire arterial tree.

Summary

A patient being treated for chronic renal failure developed massive generalized arterial calcification with obliteration of peripheral pulses and extensive cutaneous gangrene. Careful postmortem examination of his arterial tree revealed a lesion that may be related to uremia. There was widespread calcific infiltration of the media of large and small arteries along with intimal

swelling. Arterial occlusions occurred without evidence of significant atherosclerosis or thrombosis. The vascular insufficiency resulting from this lesion may have been instrumental in multiorgan failure.

REFERENCES

- 1 Faritt A M. Soft tissue calcification in uremia. *Arch Intern Med* 124:544 1969
- 2 Mallick N I and Berlyne G M. Arterial calcification after vitamin D therapy in hyperphosphatemic renal failure. *Lancet* 2:1316 1968
- 3 Friedman S A, Novack S and Thomson G L. Arterial calcification and gangrene in uremia. *N Engl J Med* 280:1392 1969
- 4 Masary S G, Gordon A, Coburn J W, Kaplan I, Franklin S, Maxwell M H and Klee-man C R. Vascular calcification and peripheral necrosis in a renal transplant recipient. *Am J Med* 49:416 1970
- 5 Richardson J A, Heron G, Reitz R and Layzer R. Ischemic ulceration of skin and necrosis of muscle in azotemic hyperparathyroidism. *Ann Intern Med* 71:129 1969
- 6 Johnson C, Graham C H and Curtis F K. Roentgenographic manifestations of chronic renal disease treated by periodic hemodialysis. *Am J Roentgenol* 101:915 1967
- 7 Schupak L and Merrill J J. Experience with long term intermittent hemodialysis. *Ann Intern Med* 62:509 1965
- 8 Katz V I, Hamper C L, Wilson M E, Bernstein D S, Wachman A and Merrill J P. The place of subtotal parathyroidectomy in management of patients with chronic renal failure. *Trans Am Soc Artif Intern Organs* 13:376 1968
- 9 Bogdanoff M D, Wood A H, White J L and Enck F L. Hyperparathyroidism. *Am J Med* 41:583 1956

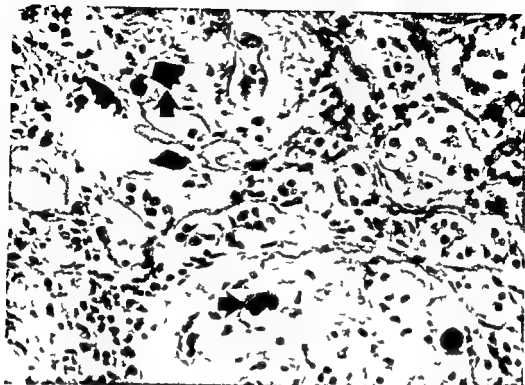


Fig. 5 Section of kidney shows diffuse tubular (↑) and glomerular calcification (→) (Hematoxylin and eosin $\times 50$)

parathyroid activity, hypoproteinemia and elevated serum phosphate levels—factors which alter calcium homeostasis. Chronic acidosis might lead to demineralization of bone with release of calcium into the blood and subsequent deposition in vessel walls, but this effect may be offset by the increased solubility of calcium salts in a more acidic blood.

In long standing renal failure parathyroid gland hyperplasia is very common but obvious vessel calcification is seen much less often. In a survey of 20 patients maintained with chronic hemodialysis arterial calcification was found in only eight of 15 patients with evidence of active hyperparathyroidism (persistent elevation of the serum alkaline phosphatase concentration).⁴ Furthermore, Katz and associates⁸ have reported very little change in vascular calcification in four patients after parathyroidectomy despite impressive resorption of other metastatic deposits. On the other hand, Massry and colleagues⁹ reported a patient who developed vessel calcification and digital gangrene following renal transplantation and demonstrated first clinical and, later, radiologic improvement after subtotal parathyroidectomy.

Our patient did not show radiologic or

histologic evidence of osteodystrophy and had only minimal elevation of the serum alkaline phosphatase concentration. However, in the presence of hypoproteinemia a serum calcium level as high as 10.6 mg per 100 ml suggests that the ionized calcium level may have been slightly elevated. Patients with primary hyperparathyroidism only rarely develop extensive arterial calcification despite much higher calcium levels than those seen in secondary hyperparathyroidism.⁹ This difference may be related to the serum phosphate concentration which is decreased in primary and elevated in secondary hyperparathyroidism. It is logical to presume that the resulting high molar product of calcium and phosphate in uremia might exceed the solubility product of calcium phosphate favoring its precipitation in soft tissues. If the phosphate concentration is a determining factor in this calcific process then its level should be carefully monitored and excess levels reduced by administration of aluminum hydroxide gels or by dialysis. Studies are in progress to evaluate this point.

In our patient the clinical significance of calcific involvement of the arterial circulation did not become apparent until a

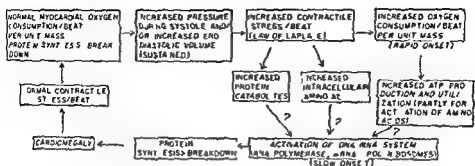


Fig. 1 Scheme illustrating the development of cardiomegaly as a negative feedback mechanism to restore myocardial energy expenditure per beat under circumstances that cause a sustained increase. The structural adaptation serves to prevent early failure of the myocardium.

above in brief I favor the first of the above mentioned alternatives although admittedly the supporting evidence is somewhat circumstantial.

With these introductory remarks as a background we might consider the most likely pathophysiologic mechanism underlying the development of hypertrophy in a certain number of cases of coronary artery disease and/or myocardial infarction associated with long term survival. Obviously other causes of cardiac hypertrophy including hypertension which favors the development of coronary atherosclerosis are excluded from consideration.

Incidence of hypertrophy

The incidence of cardiac hypertrophy in coronary atherosclerosis and myocardial infarction (in the absence of hypertension and other causes of hypertrophy) has been the subject of some controversy. In some studies the absence of arterial hypertension has been in doubt because with the onset of infarction blood pressure can fall to normal levels and may never regain its original values. Other studies have been based on roentgenologic examination of the cardiac shadow without the use of contrast media.¹¹⁻¹⁴ Such reports must be excluded since dilatation and hypertrophy cannot be distinguished by this means. Postmortem studies are essential and the absolute heart weight or better the heart weight to body weight ratio and microscopic measurements of fiber diameter are still the best available means for assessing the existence of myocardial hypertrophy (provided that cellular hydration or edema is ruled out or

accounted for). A further consideration is the number of cases reported in a given study. Older literature has been particularly prone to draw conclusions on the basis of a small number of cases examined.

Gross and associates¹⁵ reviewed the necropsy reports of 8500 cases from several hospitals and sorted out those with coronary atherosclerosis and myocardial infarction in the absence of hypertension, nephrosclerosis and diabetes. Analysis of the data led them to the conclusion that myocardial infarction is probably not causally related to cardiac hypertrophy. Miller and Weiss¹⁶ studied 19 cases of advanced coronary disease with scattered areas of fibrosis and various degrees of multiple infarction and found none to have cardiac hypertrophy on the basis of the absolute heart weight. They emphasized the view that indisputable and advanced coronary disease need not lead to gross cardiac hypertrophy. Bell and Clawson¹⁷ studied hypertensive heart disease and maintained that coronary disease by itself did not cause cardiac hypertrophy. Other observers were unable to find a relationship between myocardial fibrosis due to coronary disease and cardiac hypertrophy.¹⁸⁻²⁰ In contrast to these studies many investigators have reported the occurrence of cardiac hypertrophy (findings based on postmortem observations) in a certain percentage of patients with marked coronary atherosclerosis with or without infarction who had no evidence of chronic hypertension or other diseases that would have caused hypertrophy of the heart.²¹

Current opinion favors the view that a

Pathogenesis of cardiac hypertrophy in coronary atherosclerosis and myocardial infarction

Henry S Bader, MD
Omaha Neb

The problem of the pathogenesis of cardiac hypertrophy like most others may be likened to a jigsaw puzzle. The solution of such a puzzle tends to be more difficult at the start and gets easier toward the end when the parts begin to fit together in rapid succession. It may be fair to state that in recent years the numerous components of the puzzle of cardiac hypertrophy seem to be falling rapidly into their proper places to complete the picture. The pathogenic sequence of events leading to myocardial hypertrophy is now understood better than ever before. I have schematically outlined this in a recent Symposium on Hypertrophy of Heart Muscle.¹ A modified version of the scheme is presented in Fig. 1. Hypertrophy is regarded as a negative feedback mechanism to restore to normal the energy expenditure of a unit mass of muscle per beat whenever there is a sustained increase in stroke energy expenditure per unit mass of myocardium.^{2,3} The functional value of this structural adaptation is to prevent the early failure of the heart in chronic conditions which tend to exhaust the energy reserves of the myocardium. Current thinking has brought to focus the importance of increased mean contractile 'stress' (or tension) developed per beat as a major (but not the sole) determinant of stroke energy expenditure

of the myocardium.^{4,5} There is a host of pathologic conditions, both intrinsic and extrinsic to the heart, that might limit about such a sustained increase in contractile stress of the myocardium. During the last decade considerable progress has been made at the biochemical level in understanding the molecular events which accelerate myocardial protein synthesis during the development of hypertrophy.⁶⁻¹⁰ However, it is still uncertain what the exact mechanism is for causing an increase in myocardial protein synthesis. The following views have been proposed without convincing experimental evidence in favor of any one of them: (1) Increased production and utilization of energy rich phosphates (ATP, CP) stimulate protein synthesis probably by "activating" the amino acids and nucleotides.^{11,12} (2) Increased breakdown of cardiac proteins produces macromolecules which may inactivate repressors synthesized by a regulating gene and thereby activate the synthesis of mRNA and myocardial proteins.¹³ (3) Increased myocardial intracellular amino acid pool stimulates protein synthesis.¹⁴ (4) Decreased myocardial intracellular PO_2 may somehow stimulate protein synthesis.¹⁵ The arguments for or against each of these views have been discussed by me in the paper presented at the Symposium referred to

From the Department of Physiology and Pharmacology, Creighton University School of Medicine, Omaha, Neb.
Received for publication April 5, 1972.
Reprint requests to Henry S. Bader, MD, Department of Physiology/Pharmacology, Creighton University School of Medicine, Omaha, Neb. 68131.

case requires an understanding of the many variables which may play a part in the evolution of the vascular and myocardial pathology (1) Variability in the anatomy of the coronary arteries in man both in size and in pattern is frequent⁴ (2) Coronary atherosclerosis is rarely limited to one artery. More often than not it is distributed over a number of vessels. Thus the location with respect to the size of the vessels and the number of diseased vessels will influence the clinical and pathologic course of events (3) The enlargement of anastomotic vessels during the progressive narrowing of the affected vessels plays a very important part in the evolution of the disease. The degree of narrowing of the arteries and the rapidity with which the occlusion progresses will have a profound effect on the establishment of collateral circulation and on the coronary capillary flow to the area supplied by the collateral vessels (4) The possible involvement of the collateral vessels themselves in the atherosclerotic process must also be taken into account.

Pathologists believe that severe coronary atherosclerosis with narrowing but without complete occlusion of the lumen may cause focal or disseminated destruction of muscle tissue with fibrosis. This is presumably due to localized ischemia but there is no direct evidence to support this contention. Over all coronary flow by the N_2O method is normal in subjects with coronary artery disease under resting conditions^{43, 44} Such patients have also exhibited normal increases in coronary flow during exercise or during administration of isoproterenol or epinephrine.⁴⁵ Unfortunately reliable methods are not available at the present time for the detection of diminished blood flow in localized areas of the myocardium in the closed chest animal or man.⁴⁶ In other instances prolonged coronary insufficiency without occlusion may cause localized or extensive subendocardial necrosis of the left ventricle and papillary muscles. Lesions of the papillaries are known to be central in origin⁴⁷ which would play a role in the development of hypertrophy of the left ventricle. According to some the subendocardial localization of lesions in such cases is the result of normally poor circulation to these regions due

to the high intramyocardial pressure and extravascular compression.^{48, 49} Kirk and Hong⁵ and Moss⁵⁰ have shown that a low myocardial PO_2 prevails in these regions as compared with epicardial. Whether this is or is not due to a relatively poor circulation or to a higher metabolic rate or to both remains uncertain. According to Sonnenblick⁵¹ the endocardial layers of the left ventricle should, theoretically at least have a greater O_2 consumption than the epicardial layers.

There is considerable clinical evidence to suggest that chronic myocardial ischemia resulting from coronary atherosclerosis or from anomalous origin of the left coronary artery from the pulmonary artery causes cardiac dilatation. In anomalous origin of the left coronary artery there is hypoxemia of the perfusing blood in addition to ischemia of the left ventricle due to low perfusion pressure. In many cases the anastomotic channels between the right and the left coronary arteries are enlarged and blood flows from the aorta (high pressure) through the right coronary to the left coronary and retrograde into the pulmonary artery (low pressure).⁵² In these cases the left ventricle is markedly dilated and hypertrophic with areas of fibrosis and endocardial fibroelastosis.^{53, 54}

The exact mechanism of cardiac dilatation in chronic myocardial ischemia is not clear. One possibility is that chronic myocardial ischemia or hypoxia in localized areas increases the diastolic compliance of the cardiac chamber. Reliable data on this important problem are not available. It is more likely that coronary atherosclerosis with myocardial fibrosis causes ventricular dilatation by inducing a low grade failure of contractile function of the ventricle. Nakhjavan and co-workers⁵⁵ have demonstrated depressed contractility in isolated muscles from chronically ischemic myocardium of dogs whose coronary arteries were gradually constricted with Ameroid. Whatever the intimate mechanism for the dilatation is it is well known that dilatation increases the contractile stress (tension) of the myocardium per beat in accordance with the law of Laplace for a given intraventricular pressure.^{56, 57} This would lead to increased stroke energy expenditure per unit mass of heart muscle and cardiac

cert an proportion of patients with marked atherosclerosis and/or myocardial infarction develops cardiac hypertrophy in the absence of hypertension or other conditions that cause cardiac hypertrophy. According to Friedberg,⁴⁴ cardiac enlargement or hypertrophy occurs in at least two thirds of the patients who survive myocardial infarction due to coronary occlusion. This relatively high incidence includes subjects with hypertensive coronary disease. Investigators who have excluded hypertensive coronary disease in their studies find a lower incidence of cardiac hypertrophy in subjects who have primary atherosclerosis of the coronaries. At present, no reliable figure may be quoted to indicate the incidence of hypertrophy in primary coronary disease.

Pathogenesis

The question is posed: What is the pathogenesis of hypertrophy in these cases? Unfortunately, experimental studies to answer this question have been remarkably few. The cardiodynamic and physiologic parameters that have to be measured during the development of hypertrophy after experimental coronary occlusion are many and varied. Fundamental studies on cardiac dynamics and metabolism are difficult to perform over a period of time in animals with chronic conditions. Thus we are left with a paucity of basic data from which to draw firm conclusions about the pathogenesis.

Experimental studies

Smith,³⁶ in 1918 ligated the left anterior descending coronary artery in a few dogs and reported right ventricular hypertrophy on postmortem examination. On the other hand, Sutton and Davis³⁷ ligated the anterior descending coronary artery in 5 dogs and excised the animals on a treadmill postoperatively for periods varying from 23 to 319 days; no evidence of enlargement of the heart was found by plain x-ray examination (heart weights were not reported). The authors concluded that infarction per se does not cause cardiac hypertrophy. It should be noted that this type of radiologic evidence for or against hypertrophy is at best unsatisfactory. Whether exercise did or did not play any role in preventing the enlargement of the heart under these ex-

perimental conditions must also be taken into account. Katz and associates³⁸ induced atherosclerosis in rabbits by feeding cholesterol to them; the atheromatous process in these animals involved the coronary arteries as well as other vessels. The authors observed cardiac hypertrophy in a large proportion of the experimental animal as compared with controls. Microscopic studies of the myocardium revealed narrowing of the coronary arteries and areas of recent, organizing and old infarcts. There was no hypertension or valvular disease and no evidence of myocarditis. The conclusion was that atherosclerosis of the coronary arteries per se can cause cardiomegaly in rabbits. However, no data were obtained to elucidate the mechanism of cardiac hypertrophy. More recently, Norman and Coers³⁹ ligated the anterior descending coronary arteries in rats, and reported a significant increase in the weight of the heart 6 weeks or 12 weeks after operation as compared with sham-operated animals. Almost all coronary ligated animals demonstrated varying degrees of grossly visible infarcts. Gudbjarnason and co-workers⁴⁰ produced cardiac hypertrophy in dogs by placing Ameroid* constrictors around three coronary arteries in each experimental animal: right coronary at its origin, circumflex branch of the left coronary and anterior descending coronary (distal to septal branch). After 7 days there was a significant increase in the weight of the left ventricle, the right ventricle and the interventricular septum which was not ischemic.

If myocardial infarction leads to a ventricular aneurysm, there is a tendency of the noninfarcted myocardium in that ventricle to undergo hypertrophy. Tyson and co-workers⁴¹ showed that in dogs the establishment of a left ventricular aneurysmal sac made of fresh homologous thoracic arch (which is expansile) caused hypertrophy of the left ventricle within 3 to 4 weeks. If the sac was made of Teflon which is nonexpansile, the left ventricle did not hypertrophy.

Clinical observations

A discussion of the pathogenesis of myocardial hypertrophy in coronary artery dis-

*American Plastics Co. p. Bainbridge, N. J.

muscle tends to be restored to or toward normal⁴⁴ and further growth of muscle ceases. It is assumed that during the development of myocardial hypertrophy the coronary vascular system in the nonischemic regions is capable of undergoing dilatation and growth which is somewhat commensurate with the growth of the muscle. If the coronary vascular tree is incapable of such growth because of intrinsic disease quite conceivably the hypertrophy of the heart muscle may be curtailed or prevented entirely. If this concept is true one may explain at least partly why cardiac hypertrophy in coronary atherosclerosis is not so frequent as might be expected. Some clinical data however seem to support this concept. For instance Jones³² observed that in hypertensive patients cardiac hypertrophy was least pronounced when there was accompanying severe coronary atherosclerosis. A similar view was expressed by Bell and Clawson.⁴⁵

The interesting observations of Gudbjarnason and associates⁴⁶ who noted myocardial hypertrophy in diffusely ischemic ventricles (induced by Ameroid constrictors) as well as in the nonischemic septum of the dog heart are difficult to explain. In these studies data such as heart rate, end-diastolic volume, left ventricular coronary flow and oxygen consumption were lacking. The possibility of damage and edema in the ischemic areas was not ruled out.

As was pointed out earlier many variables are involved in the development of myocardial hypertrophy in disease of the coronary arteries. This fact may explain why many patients do not develop cardiac hypertrophy. Such patients are generally those who do not exhibit congestive failure or cardiac dyspnea prior to death from the disease. Furthermore the failure to find an increase in the total mass of a cardiac chamber in advanced coronary disease may be partly due to the fact of replacement of muscle tissue by fibrous tissue (decreased total mass of muscle by scarring) especially when there are multiple healed infarcts with thinning of the ventricular wall. This may account for the lack of hypertrophy as judged from the absolute weight of the heart in some cases.

Summary

The pathogenesis of cardiac hypertrophy is now understood better than ever before. Hypertrophy is initiated either by a sustained increase in mean contractile stress (or tension) or more likely, by a sustained increase in stroke energy expenditure of a unit mass of heart muscle. Myocardial hypertrophy occurs in a certain percentage of patients with coronary atherosclerosis and/or myocardial infarction in the absence of arterial hypertension or other diseases which cause cardiac hypertrophy. The pathogenesis under these circumstances seems to be causally related to dyssynergy and dilatation of the cardiac chamber. These changes may be caused by chronic localized ischemia of the myocardium with diffuse fibrosis (without complete occlusion) or by congestive failure arising from acute infarction and necrosis. Dyssynergy and dilatation of a cardiac chamber increase the mean contractile stress per beat and the stroke energy expenditure of the non-ischemic myocardium which subsequently undergoes hypertrophy. It has been postulated that the regions which hypertrophy must be capable of undergoing the vascular enlargement that accompanies hypertrophy of cardiac muscle and that vascular disease may curtail this. In many cases of coronary atherosclerosis and infarction the changes described may not occur and hypertrophy will not develop if other causative factors of hypertrophy (e.g. hypertension) are absent.

REFERENCES

1. Bader H S. Initiation of myocardial hypertrophy in health and in disease. In Barta E. editor. Hypertrophy of heart muscle. Bratislava Czechoslovakia Folia Fac Med Univ Comenianae Bratisl. Vol 10 Suppl 1977 (In press).
2. Bader H S. Biological significance of cardiac hypertrophy. *Am J Cardiol* 14:133 1964.
3. Bader H S. Metabolic basis of cardiac hypertrophy. *Progr Cardiovasc Dis* 11:53 1968.
4. Sarnoff S J, Braunwald E, Welch G H Jr, Case R B, Stain W N and Macruz R. Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension time index. *Am J Physiol* 192:148 1958.
5. Rodbard S, Williams F and Williams C. The physical dynamics of the heart (myocardial tension, oxygen consumption, coronary

hypertrophy would ensue. It is reasonable to expect that in advanced coronary atherosclerosis the increase in myocardial energy expenditure and hypertrophy is confined to areas of muscle which are well perfused with blood and are capable of undergoing the vascular changes that occur with the onset of myocardial hypertrophy. The vascular changes have been extensively studied in cardiac hypertrophy induced by various means. I have reviewed this problem recently.⁸⁴ Presumably, the vascular dilatation and growth that occur in cardiac hypertrophy are associated with the increased metabolic rate of the myocardium during the period of adaptive growth of the muscle. The development of hypertrophy does not necessarily ensure that the contractile function and energetics of the cardiac chamber are completely restored to normal particularly when the coronary arteries are narrowed. Despite the hypertrophy there may be signs of low grade failure which would tend to further dilate the heart and aggravate the situation in the form of a positive feedback mechanism.

When acute infarction supervenes on an atherosclerotic coronary arterial tree an acute cardiac failure may or may not develop depending upon the size and the location of the infarct. The latter may cause A-V block, bundle branch block, papillary muscle dysfunction, mitral regurgitation, etc. In the presence of acute failure the end diastolic volume of the heart is increased and the heart is dilated.⁸⁵ There is reduction in stroke volume and cardiac output. Tachycardia may prevail.^{86, 88} Fenrant and Wiggers⁸⁹ and others^{90, 91} have shown that the acutely infarcted muscle stops contracting soon after coronary ligation and bulges out during systole. This has been described as dyssynergy of ventricular contraction by Langley and co-workers⁹² or asynergy of contraction by others.^{93, 95} The passive stretch of the noncontracting infarcted muscle requires that the well perfused regions of the muscle shorten to a greater extent than normal in order to raise the ventricular pressure sufficiently to open the semilunar valves and eject blood. Hood and Whiting⁹⁶ have calculated the degree of shortening of noninfarcted fibers in dogs

1 to 7 days after ligating the coronary artery and reported an increased shortening as compared with that of sham-operated dogs. Nakano⁹⁷ and West⁹⁸ have shown, with the strain gauge arch, that the contractile force of the well perfused regions of the myocardium is augmented. Langley and co-workers⁹⁹ refer to this effort of the heart as 'wasted internal work,' a concept that is in accord with modern views of the total work of the contractile elements of heart muscle.^{100, 101} As a consequence, there will be an increase in the energy expenditure per beat of the "contractile elements" in the well perfused regions of the affected chamber. This metabolic change is believed to lead to hypertrophy of the noninfarcted muscle of the chamber. Guderham and associates¹⁰² ligated several branches of the left coronary artery in dogs and noted an increase in protein synthesis in the noninfarcted regions of the left ventricle during a period of 10 days that was studied after infarction. The observations of Busch¹⁰³ lend further support to this concept. He observed that in massive infarctions of the left ventricle there was marked hypertrophy of the perfused myocardium in the free wall of the left ventricle. He described this compensatory growth as a vicious hypertrophy. Hypertrophy will be pronounced if the infarcted area is large or is in a critical part of the myocardium that causes other functional disturbances such as papillary muscle dysfunction with mitral regurgitation, etc. If an aneurysm develops in the area of infarction it will likewise augment the energy expenditure of the muscle fibers in the well perfused regions of the heart.

If there is sufficient damage to ventricular muscle tissue or if there is a persistent functional disturbance (e.g. papillary dysfunction) there may be clinical signs of chronic congestive failure with dilatation of the heart. These cases show the most pronounced hypertrophy on postmortem examination. Most investigators agree that chronic congestive failure is an important precursor of cardiac hypertrophy in cases of myocardial infarction or severe coronary atherosclerosis.^{47, 2, 5}

When cardiac hypertrophy attains a certain level the aerobic energy expenditure (oxygen consumption) per unit mass of

- 40 Weiss M M and Weiss M M Jr Effect of myocardial infarction on size of heart *Am J Med Sci* 231:179 1957
- 41 Gross H J, Fezer A, Somborg A and Palm E B The infrequency of uncomplicated coronary artery disease and myocardial infarction as causes of cardiac hypertrophy and death based on a survey of 8 500 necropsies *New York J Med* 53:158 1953
- 42 Miller H R and Weiss M M Disease of the coronary arteries Its occurrence without gross cardiac hypertrophy *Arch Intern Med* 89:4 1928
- 43 Bell E T and Clawson B J Primary (essential) hypertension A study of four hundred and twenty cases *Arch Path* 30:939 1978
- 44 Nathanson M H Disease of the coronary arteries. Clinical and pathological features *Am J Med Sci* 150:240 1975
- 45 Liss J R and Rimm A Myocardial infarction or gross fibrosis Analysis of one hundred necropsies *Arch Intern Med* 103:131 1957
- 46 Bartels E C and Smith H I Gross cardiac hypertrophy in myocardial infarction *Am J Med Sci* 184:452 1953
- 47 Davis D and Blumgart H L Cardiac hypertrophy Its relation to coronary arteriosclerosis and congestive heart failure *Ann Intern Med* 11:1074 1937
- 48 Shohet A S, Trub S J and Kupersmith H Studies in coronary disease Relation of coronary sclerosis to heart weight and to right and left ventricular hypertrophy *Illness Med J* 240 1940
- 49 Friedman C E Heart volume myocardial volume and total capacity of the heart cavities in certain chronic heart diseases *Acta Med Scand* 180 (Suppl 257) 74 1951
- 50 Connolly E I and Littmann D Coronary arteriosclerosis and myocardial hypertrophy *New Eng J Med* 240:753 1951
- 51 Busch W Die vikariierende Hypertrophie in der linken Herzkammer *Cardiologia (Basel)* 2:366 1953
- 52 Ellis L B, Allison R B, Rodriguez F L and Robbins S L Relation of the degree of coronary artery disease and of myocardial infarction to cardiac hypertrophy and congestive heart failure *New Eng J Med* 266:925 1962
- 53 Van Peenen H and Gursel B Arteriosclerotic massive hypertrophy of the heart *J Am Geriatr Soc* 10:505 1962
- 54 Zano E C and Tabor S H Cardiac hypertrophy in acute myocardial infarction A study based on 100 autopsied cases *Circulation* 28:1081 1963
- 55 Friedberg C K Diseases of the heart ed 3 Philadelphia 1966 W B Saunders Co p 190
- 56 Smith F M The ligation of coronary arteries with electrocardiographic study *Arch Intern Med* 88:3 1918
- 57 Smith D C and Dax M D Effects of exercise on experimental cardiac infarction *Arch Intern Med* 88:1118 1931
- 58 Katz L N, Sanders A, Megibow R S and Carlen S Heart size and experimental atherosclerosis in the rabbit *Am J Med Sci* 200:731 1910
- 59 Norman T D and Coers C R Cardiac hypertrophy after coronary artery ligation in rats *Arch Path* 69:181 1960
- 60 Gudbjarnason S, Bransch W and Binn R J Protein synthesis in cardiac hypertrophy and heart failure in Reindell H Keul J and Dull E editors Heart failure pathophysiological and clinical aspects Stuttgart 1968 G Thume Verlag 184
- 61 Tyson K, Mandelbaum I and Schumacker H B Jr Experimental production and study of left ventricular aneurysms *J Thorac Cardiovasc Surg* 44:31 1967
- 62 Baridi G and Scmazzone G Coronary circulation in the normal and the pathologic heart Washington 1967 United States Government Printing Office p 35-43
- 63 Holmberg S, Laulin S, Erikovky I and Varnauka L Coronary blood flow in man and its relation to the coronary arteriogram *Am J Cardiol* 19:486 1967
- 64 Rowe G C, Thomson J H, Stenlund R R, McKenna D H, Walter D and Corliss R J A study of hemodynamics and coronary blood flow in man with coronary artery disease *Circulation* 39:139 1969
- 65 Gorlin R Physiologic studies in coronary atherosclerosis *Fed Proc* 21 (Part 2 suppl) 2:93 1962
- 66 Cohen I, Elliott W C, Klein M H and Gorlin R Coronary heart disease Clinical cinearteriographic and metabolic correlations *Am J Cardiol* 17:153 1966
- 67 Sullivan J M and Gorlin R Effect of isoprenaline on coronary circulation in human subjects with and without coronary artery disease *Circ Res* 21:919 1967
- 68 Rees J R Radio-isotopes and regional blood flow *Br Heart J* 32:137 1970
- 69 Burch G E, DePasquale N I and Phillips J H The syndrome of papillary muscle dysfunction *Am Heart J* 63:399 1968
- 70 Estes M H, Entman M L, Dixon H H and Hackett D H The vascular supply of the left ventricular wall *Am Heart J* 71:58 1966
- 71 Hong C M, Kirk E S and Myers W W Transmural distributions of blood flow, oxygen tension and metabolism in myocardium Mechanism and adaptations in Marchetti G and Taccardi B editors Coronary circulation and energetics of the myocardium Basel and New York 1967 S Karger AG p 31
- 72 Kirk E S and Hong C R Nonuniform distribution of blood flow and gradients of oxygen tension within the heart *Am J Physiol* 207:661 1964
- 73 Moss A J Intramyocardial oxygen tension *Cardiovasc Res* 2:314 1968
- 74 Sonnenblick E H Comment on papers by Repton Hong and Myers in Marchetti G and Taccardi B editors Coronary circulation and energetics of the myocardium Basel and New York 1967 S Karger AG p 52
- 75 Salustian D C Jr, Neill C A and Tausig H B The direction of blood flow in anomalous

- flow and efficiency) *Am Heart J* 57:318 1959
- 6 Kitz I N and Lemberg H The relation of cardiac effort to myocardial oxygen consumption and coronary flow *Circ Res* 6:656 1958
 - 7 Lendrum B Lemberg H and Kitz I N The oxygen consumed and pressure developed by the dog's left ventricle at different end diastolic volumes *Acta Cardiol* 16:487 1961
 - 8 Lemberg H Kitz I N and Boyd I Determinants of coronary flow and myocardial oxygen consumption *Am J Physiol* 202:45 1962
 - 9 Rodbard S William C B Rodbard D and Berglund L Myocardial tension and oxygen uptake *Circ Res* 13:139 1964
 - 10 Rolett L L Yurchak P M Hood W B Jr and Gorlin R Pressure-volume correlates of left ventricular oxygen consumption in the hypervolemic dog *Circ Res* 17:499 1965
 - 11 McDonald R H Jr Developed tension: A major determinant of myocardial oxygen consumption *Am J Physiol* 210:351 1966
 - 12 McDonald R H Jr Taylor R B and Cingolani H E Measurement of myocardial developed tension and its relation to oxygen consumption *Am J Physiol* 211:667 1966
 - 13 Graham T P Jr Covell J W Sonnenblick E H Ross J Jr and Braunwald E Control of myocardial oxygen consumption: Relative influence of contractile state and tension development *J Clin Invest* 47:375 1968
 - 14 Braunwald E The determinants of myocardial oxygen consumption *Physiol* 12:65 1969
 - 15 Badier H S Work and energy expenditure of the heart *Acta Cardiol* 24:227 1969
 - 16 Meerson I Z Alchimi G M Aleksandrov P N and Bazardjan A G Dynamics of nucleic acid and protein synthesis of the myocardium in compensatory hyperfunction and hypertrophy of the heart *Am J Cardiol* 22:337 1965
 - 17 Tomita K Studies on myocardial protein metabolism in cardiac hypertrophy *Jap Heart J* 7:566 1966
 - 18 Moroz L A Protein synthetic activity of heart microsomes and ribosomes during left ventricular hypertrophy in rabbits *Circ Res* 21:449 1967
 - 19 Schreiber S S Oratz M and Rothschild M A Protein synthesis in the overloaded mammalian heart *Am J Physiol* 211:314 1966
 - 20 Schreiber S S Oratz M and Rothschild M A Effect of acute overload on protein synthesis in cardiac muscle microsome *Am J Physiol* 213:1552 1967
 - 21 Schreiber S S Oratz M Evans C Silver E and Rothschild M A Effect of acute overload on cardiac muscle mRNA *Am J Physiol* 215:1250 1968
 - 22 Schreiber S S Oratz M and Rothschild M A Nuclear RNA polymerase activity in acute hemodynamic overload in the perfused heart *Am J Physiol* 217:1305 1969
 - 23 Morkin I and Ashford T I Myocardial DNA synthesis in experimental cardiac hypertrophy *Am J Physiol* 215:1409 1968
 - 24 Lemberg H and Pomer B I Laboric acid synthesis in experimental cardiac hypertrophy in rats I Characterization and kinetics of labeling *Circ Res* 23:173 1968
 - 25 Kaku I Study of the myocardial nucleic acids and proteins metabolism in experimentally induced cardiac hypertrophy on heart failure *Jap Heart J* 9:293 1968
 - 26 Nair K G Cutler A F Zak R Kode T and Kabinowitz M Biochemical correlates of cardiac hypertrophy I Experimental model changes in heart weight RNA content and nuclear RNA polymerase activity *Circ Res* 23:451 1968
 - 27 Kode T and Kabinowitz M Biochemical correlates of cardiac hypertrophy II Increased rate of RNA synthesis in experimental cardiac hypertrophy in the rat *Circ Res* 24:9 1969
 - 28 Grove D Nair K G and Zak R Biochemical correlates of cardiac hypertrophy III Change in DNA content the relative contributions of polyploidy and mitotic activity *Circ Res* 23:463 1969
 - 29 Grove D Nair K G and Vachentrone V Biochemical correlates of cardiac hypertrophy IV Observations on the cellular organization of growth during myocardial hypertrophy in the rat *Circ Res* 23:473 1969
 - 30 Ito Y Matsumoto S Kaku I and Kozuma T Protein and nucleic acids of rabbit heart muscle in experimentally produced cardiac hypertrophy and failure *Israel J Med Sci* 5:501 1969
 - 31 Durr C H and Hollnagel J O Hypertrophied non-failing rat heart *Circ Res* 23:45 1969
 - 32 Meerson F I The myocardium in hyperfunction hypertrophy and heart failure *Circ Res* 24 and 25 (Suppl II) II 88 114 1969
 - 33 Cohen J Feldman R E and Whitbeck A A Effects of energy availability on protein synthesis in isolated rat atria *Am J Physiol* 216:76 1969
 - 34 Meerson F I The myocardium in hyperfunction hypertrophy and heart failure *Circ Res* 24 and 25 (Suppl II) II 98 1969
 - 35 Wannemacher R W Jr and McCoy J R Regulation of protein synthesis in the ventricular myocardium of hypertrophic hearts *Am J Physiol* 216:781 1969
 - 36 Hollenberg V Stenzel K H and Puhm A L Hypoxia: A stimulus to myocardial cell growth *Circulation* 35 and 36 (Suppl II) II 143 1967 (abstract)
 - 37 Parkinson J Enlargement of the heart *Lancet* 1:1391 1936
 - 38 Palmer J H The size of the heart after coronary thrombosis *Canad Med Ass J* 26:381 1937
 - 39 Master A M Etiology of cardiac enlargement in coronary occlusion hypertension and coronary artery disease *Am Heart J* 4:131 1954

Fundamentals of clinical cardiology

Functional diastolic murmurs

Aldo I. Luisada, MD

Mahmoud A. I. Durrani, MD, PhD, MRCP

Chicago, Ill

Diastolic murmurs not caused by valve lesions and thus termed functional have been described for a long time. Probably the first to be described was the Austin Flint low frequency apical rumble of aortic insufficiency.¹ This was followed by the Graham Steell high frequency basal blowing murmur caused by pulmonary hypertension in mitral stenosis² and by the midprecordial or apical Carey Coombs murmur of acute rheumatic fever.³ Since then, functional diastolic murmurs have been described in pericardial and hypertensive heart diseases,⁴ acute rheumatic fever without mitral stenosis,⁵ and myocarditis.⁶ Subsequently phonocardiographic studies documented such murmurs in rheumatic coronary hypertension and congenital heart diseases.⁷⁻¹¹ In particular certain diastolic phenomena of mitral insufficiency¹²⁻¹⁷ (occasional opening snap, frequent third sound and nearly as frequent middiastolic rumble) have a special importance because of possible misdiagnosis of double mitral defect. It is of interest that occasional diastolic murmurs (if both low and high frequency) can be found in graphic tracings of normal individuals even though such murmurs are not common on auscultation.^{18,19}

In spite of repeated statements and pub-

lications on this subject including several from our group^{17,19-22} teaching in several medical schools still persists in stating that all apical diastolic murmurs are caused by mitral stenosis thus perpetuating an erroneous concept.

For this reason we shall present a few tracings obtained in a variety of conditions in order to re-emphasize the frequent occurrence of apical diastolic murmurs in patients without mitral stenosis. Among them the most important because they are the most misleading are those in patients with rheumatic carditis, mitral insufficiency, myocarditis or cardiomyopathy, pulmonary heart disease or coronary heart disease.

Case reports

Case 1. The patient was a 16-year old boy examined six months after the onset of the first attack of rheumatic fever. At the time of recording there was no fever or joint involvement but the patient was weak, the heart rate was rapid, the sedimentation rate was high and the C-reactive protein titer was still elevated. The electrocardiogram (ECG) showed a P-R interval lasting 0.20 sec. (slightly prolonged for the age). Heart rate was 100 beats per minute and blood pressure was 175/60. The heart was enlarged and both a systolic and a diastolic murmur were prominent. There was a Grade 2 blowing systolic aortic murmur and an apical diastolic presystolic murmur.

The phonocardiogram (Fig. 1) showed a diamond shaped systolic murmur and a middiastolic rumble

1. The Department of Cardiology (Medical) of Chicago Medical School University Health Science and The Medical Clinics, Hospital Medical Center, Chicago, Ill.
2. The patient was dead at the time of the study.
3. The patient was dead at the time of the study.
4. The patient was dead at the time of the study.
5. The patient was dead at the time of the study.
6. The patient was dead at the time of the study.
7. The patient was dead at the time of the study.
8. The patient was dead at the time of the study.
9. The patient was dead at the time of the study.
10. The patient was dead at the time of the study.
11. The patient was dead at the time of the study.
12. The patient was dead at the time of the study.
13. The patient was dead at the time of the study.
14. The patient was dead at the time of the study.
15. The patient was dead at the time of the study.
16. The patient was dead at the time of the study.
17. The patient was dead at the time of the study.
18. The patient was dead at the time of the study.
19. The patient was dead at the time of the study.
20. The patient was dead at the time of the study.
21. The patient was dead at the time of the study.
22. The patient was dead at the time of the study.

- left coronary artery arising from the pulmonary artery. *Circulation* 22:591 1960
- 76 Keith J D The anomalous origin of the coronary artery from the pulmonary artery. *Br Heart J* 21:149 1959
 - 77 Nadas A S Gombor R and Hugenholz P G Anomalous left coronary artery originating from the pulmonary artery. Report of two surgically treated cases with a proposal of hemodynamic and therapeutic classification. *Circulation* 29:167 1964
 - 78 Bookstein J J Aberrant left coronary artery. *Am J Roentgen* 91:515 1964
 - 79 Noren G R Raghbi G Moller J H Amplatz K Adams L Jr and Edwards J L Anomalous origin of the left coronary artery from the pulmonary trunk with special reference to the occurrence of mitral insufficiency. *Circulation* 30:171 1964
 - 80 Nishiyama I K Son R and Goldberg H Myocardial contractility in areas with chronic ischemia. Studies on isometric tension. *Circulation Res* 22:226 1968
 - 81 Burch G I Rys C I and Cronvich J A Certain mechanical peculiarities of the human cardiac pump in normal and diseased state. *Circulation* 5:504 1952
 - 82 Burton A C The importance of the shape and size of the heart. *Am Heart J* 51:801 1957
 - 83 Levine H J and Wigman R J Energetics of the human heart. *Am J Cardiol* 9:372 1962
 - 84 Badger H S Myocardial blood flow and oxygen uptake in clinical and experimental cardiomegaly. *Am Heart J* 82:105 1971
 - 85 Kazamias I M Gander M I and Ross J Jr Serial changes in left heart size in acute myocardial infarction (AMI). *Circulation* 42 (Suppl 3):171 1970 (abstract)
 - 86 Malmcrona R Haemodynamics in myocardial infarction. *Acta Med Scand* 176 (Suppl 417) 2 1964
 - 87 Thomas M Malmcrona R and Shillingford J Hemodynamic changes in patients with acute myocardial infarction. *Circulation* 31:811 1965
 - 88 Shillingford J and Thomas M Hemodynamic effects of acute myocardial infarction in man. *Progr Cardiovasc Dis* 9:571 1967
 - 89 Tennant R and Wiggers C J Effect of coronary occlusion on myocardial contraction. *Am J Physiol* 112:351 1935
 - 90 Prinzmetal M Schwartz L L Corday E Spritzler R Bergman H C and Kruer H L Studies on the coronary circulation. VI. Loss of myocardial contractility after coronary artery occlusion. *Ann Intern Med* 31:199 1949
 - 91 Fittole C J and Randall W C Lead ventricular bulging after acute coronary occlusion. *Am J Physiol* 201:431 1961
 - 92 Langley J O Martinez A Finkbein A Duvot in I and Harrison T K Intraventricular precordial motion and wasted left ventricular work. The concept of cardiac dysynergy. *Am Heart J* 73:349 1967
 - 93 Herman M V Henle R A Klein M D and Gorlin R Localized disorders in myocardial contraction: A synergy and its role in congestive heart failure. *New Eng J Med* 247:222 1967
 - 94 Herman M V and Gorlin R Implications of left ventricular synergy. *Am J Cardiol* 23:538 1969
 - 95 Kazamias I M Gander M I Loss J Jr and Braunwald E The localization of synergistic areas of left ventricular wall by radio-kymography. *Am J Cardiol* 25:108 1970 (in tract)
 - 96 Hood W B Jr and Whiting R H Experimental myocardial infarction—Increased fiber shortening in non infarcted muscle. *Clin Res* 16:514 1968 (abstract)
 - 97 Nakano J Effect of changes in coronary arterial blood flow on the myocardial contractile force. *Jap Heart J* 7:118 1966
 - 98 West J W Atrial and ventricular force of contraction influenced by intracoronary injections. *Am J Physiol* 203:1145 1967
 - 99 Britman N A and Levine H J Contractile element work. A major determinant of myocardial oxygen consumption. *J Clin Invest* 43:1397 1964
 - 100 Sonnenblick L H Series elastic and contractile elements in heart muscle. *Chin c in muscle length*. *Am J Physiol* 204:1350 1964
 - 101 Coleman H N Effect of alterations in heartening and external work on oxygen consumption of cat papillary muscle. *Am J Physiol* 211:100 1968
 - 102 Jones R S The weight of the heart and its chambers in hypertensive cardiovascular disease with and without failure. *Circulation* 7:357 1953

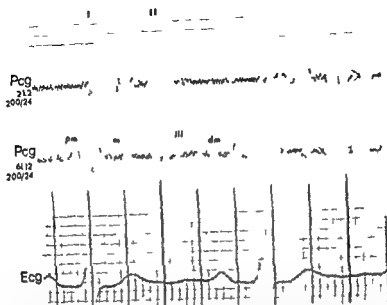


Fig. 3 Case 3—Austin Flint murmur in a 49-year-old man with rheumatic aortic insufficiency. I II III = heart sounds; ps = presystolic murmur; dm = mid-diastolic murmur; ps = presystolic murmur. The upper tracing at the second left shows better the early-diastolic murmur of aortic insufficiency. The middle tracing at the apex shows better the functional diastolic murmur.

tion showed the typical mitral systolic and aortic diastolic murmurs. When recorded without filtration (Fig. 4) the blowing murmurs were not recorded but one could see a large summation gallop sound of long duration. It was concluded that there was insufficiency of the mitral and aortic valves but no mitral stenosis. Cardiac catheterization subsequently performed excluded mitral stenosis.

Case 5 This patient was a 10-year-old Negro boy with sickle cell anemia who came to observation during a crisis with loud systolic and diastolic presystolic murmurs. The heart was severely enlarged. The question of sickle cell anemia associated with rheumatic heart disease was raised.

The laboratory data excluded active rheumatic fever. The ECG was within normal limits.

The phonocardiogram was simultaneously recorded at the base and apex. In both tracings (Fig. 5) there was a diamond-shaped systolic murmur. The second sound was prolonged at the base by an early-diastolic murmur that then continued with less amplitude throughout diastole and had a larger phase in presystole. A larger vibration at the apex was probably a high frequency third sound.

On the basis of the phonocardiographic findings the rheumatic heart disease was excluded because the murmurs were nontypical and were extremely diffuse. Six months later a new tracing was recorded when the anemia was moderate (Fig. 5) it showed only a minimal flow murmur in systole and minimal vibrations in diastole. Thus the previous diagnosis was confirmed.

Case 6 This was a 59-year-old man with a history of hypertension and evidence of minimal heart

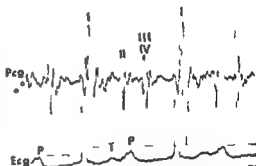


Fig. 4 Case 4—Low frequency prolonged diastolic sound (summation gallop) giving the auscultatory impression of a mid-diastolic rumble in a 76-year-old woman with mitral and aortic insufficiency. The apical tracing recorded without filtration shows the complex vibration in diastole. Grade 1 A V block causes the summation of two diastolic sounds.

failure. The heart was enlarged to both the right and left but the right side was especially dilated. The pulmonary artery and its branches were very large on x-ray and the pulmonary vasculature was engorged. On auscultation there was a crescendo-decrescendo systolic murmur at the base and a loud and split second sound and a diastolic presystolic murmur. The ECG showed biventricular hypertrophy and a Grade 1 A V block (P-R = 0.32 sec). The blood pressure was 180/110.

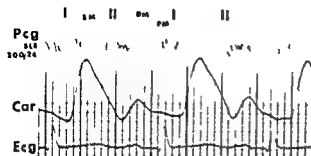


Fig. 1 Case 1—Rheumatic carditis in a 16-year-old boy. SM = systolic murmur; DM = diastolic murmur continuing in presystole (P/M); I = first sound; II = second sound; Car = carotid pulse tracing; ECG = electrocardiogram.

of high voltage continuing in presystole. One should note that the diastolic murmur started late in diastole and a crescendo-decrescendo appearance and then continued with a smaller presystolic phase that was not in crescendo. A high frequency tracing at the base revealed a mild decrescendo early diastolic murmur of small voltage.

Cardiac catheterization was not performed because of the acute condition of the patient.

Here the diagnostic problem was whether there was a functional diastolic murmur or the rumble of mitral stenosis. The latter might have been caused by a previously unrecognized attack of rheumatic fever. The absence of an opening snap and the high voltage high frequency late onset and configuration of the diastolic murmur allowed us to exclude mitral stenosis. The diastolic murmur moreover was out of proportion with the minimal aortic insufficiency and was not called in Austin Flint murmur.

The conclusion was acute rheumatic carditis, functional murmurs related to dilatation of the cardiac chambers. Such a conclusion was proved by the subsequent course of the patient as well as the unanimous opinion of several consultants.

Case 2 This patient was a 12-year-old girl with acute rheumatic fever of two weeks' duration. The general description of the disease is similar to that of the previous case. The elevated antistreptolysin O titer and C-reactive protein confirmed the diagnosis of acute rheumatic fever. The ECG revealed a Grade I A V block. On auscultation there was a Grade 2/6 pansystolic murmur and a Grade 3/6 low pitched diastolic rumble over the midprecordium. There were also a Grade 2 ejection systolic murmur and a Grade 2 blowing early diastolic murmur along the left sternal border.

At the apex the phonocardiogram (Fig. 2) showed an early and midsystolic murmur. In diastole there was a prandistolic murmur including the presystolic phase. With high frequency filtration a mild early diastolic blowing murmur was recorded at the left sternal border.

Cardiac catheterization was not performed on account of the acute condition of the patient.

The configuration and high voltage of the diastolic

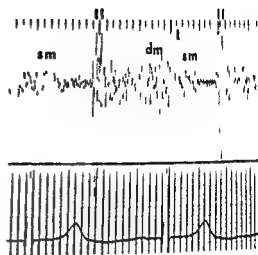


Fig. 2 Case 2—Rheumatic carditis in a 12-year-old girl. Systolic murmur in decrescendo; diastolic murmur lasting through the presystolic phase. Symbols as in Fig. 1.

murmur and the lack of opening snap allowed us to exclude mitral stenosis.

The final conclusion was functional diastolic rumble (Cox's Coombs murmur) superimposed on a murmur of moderate mitral insufficiency, but the diastolic murmur of moderate aortic insufficiency. The murmurs of valve insufficiency were probably related to valvular dilatation. The clinical picture together with the graphic tracings led to the diagnosis of acute rheumatic carditis.

Case 3 A 19-year-old man with rheumatic aortic insufficiency had a severely enlarged heart mainly due to left ventricular dilatation. There was a prolonged I K interval (0.21 sec). On auscultation both a crescendo-decrescendo systolic murmur and an early diastolic blowing murmur were heard at the base. At the apex there was a diastolic presystolic rumble similar to that of mitral stenosis.

The phonocardiogram was multaneously recorded at the base and apex. The apical tracing (Fig. 3) in addition to vibrations transmitted from the base showed a high frequency third sound and a diastolic presystolic murmur. The latter was not typically in crescendo as in mitral stenosis and was not preceded by an opening snap. Records taken at the left sternal border showed an early diastolic murmur of high frequency.

The conclusion was aortic insufficiency. An Austin Flint murmur, aortic flow murmur. Cardiac catheterization excluded mitral stenosis. Angiography revealed severe aortic insufficiency and minimal mitral insufficiency.

Case 4 This was a 26-year-old woman with a heart markedly enlarged to the left, and both an apical pansystolic murmur and a bidirectional diastolic decrescendo murmur. There was also a loud prolonged sound in diastole that gave rise to a picture of mitral stenosis in addition to mitral and aortic insufficiency. The ECG showed evidence of left ventricular hypertrophy, and Grade I A V block (I K = 0.36 sec).

The phonocardiogram with high frequency ultra-

1 cm 25
1 sec 2

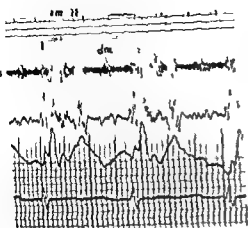


Fig 6 Case 6—High and low frequency functional diastolic murmurs in a 59 year old man with hypertensive heart disease and atrial septal defect. The upper tracing is an acceleration tracing at 100 to 100 Hz which shows mid-diastolic high frequency murmur and diamond shaped systolic murmur. The central tracing is an unfiltered velocity tracing which shows low frequency third and fourth sounds. The next tracing is an apex cardio-gram. The lower tracing is an electrocardiogram.

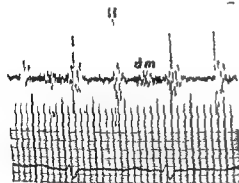


Fig 7 Case 7—Mid-diastolic presystolic rumble in a 59 year old woman with atrial septal defect (secundum type). The phonocardiogram was recorded at the apex without a filter.

of the sternum. There was a Grade 2/6 systolic murmur over the midprecordium and a third out of the heart sound. The phonocardiogram recorded in a low frequency band (Fig 10) showed good quality of the heart sound, a barely audible systolic murmur and a low frequency diastolic rumble of large voltage which was late after the second sound and late in presystole. Tricuspid regurgitation and higher frequency diastolic rumble led a close filter of the second sound with a large pulmonary component. The diagnosis was chronic cor pulmonale and functional diastolic murmur of the right heart.

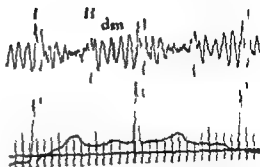


Fig 8 Case 8—Low frequency diastolic rumble in a 56-year old man with alcoholic cardiomyopathy. The tracing was recorded at the apex and is a displacement tracing at 10 to 40 Hz.

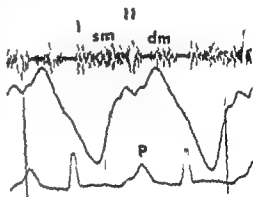


Fig 9 Case 9—Mid-diastolic high frequency murmur in a 39 year old man with chronic cor pulmonale. The upper tracing is a velocity tracing with high pass filter at 400 Hz (slope 24 db per octave) which reveals a pansystolic murmur of tricuspid insufficiency and mid-diastolic murmur. The central tracing is a jugular tracing that shows a sharp rise in systolic wave and a plateau typical of tricuspid insufficiency.

Case 11 This patient was a 63 year old man with a history of hypertension and coronary heart disease (angina pectoris). In the last few months evidence of left ventricular failure had been present. The ECG showed a Grade I A V block and evidence of left ventricular hypertrophy and strain.

Auscultation disclosed a Grade 1/6 presystolic murmur and a Grade 2/6 diastolic rumble at the apex, a Grade 2/6 systolic ejection murmur and a Grade 1/6 blowing diastolic murmur at the base.

The phonocardiogram recorded in a medium low frequency band at the apex (Fig 11) revealed a presystolic presystolic murmur, a few decrescendo vibrations in early diastole and a presystolic murmur that was increasing in some cycles. At the base there was a crescendo-decrescendo systolic murmur and a minimal decrescendo diastolic murmur.

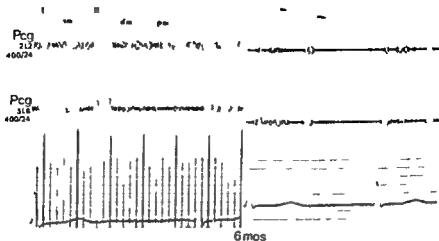


Fig. 5 Case 5—High frequency functional diastolic and presystolic murmur both at base (upper tracing) and apex (middle tracing) in a 10 year old boy with sickle cell anemia. The tracings at left were recorded during the first six months after diagnosis.

The phonocardiogram (Fig. 6) recorded over the fourth left intercostal space close to the sternum showed both a third and a fourth sound of low frequency. It also showed a very large diamond shaped systolic murmur and a diastolic presystolic murmur of high frequency. The diastolic murmur was different from that of mitral stenosis on account of its high frequency, the lack of an opening snap and the fact that it was recorded over a wide area of the precordium.

On the basis of the clinical, electrocardiographic, roentgenologic and phonocardiographic data the diagnosis of atrial septal defect and hypertensive heart disease was made. This diagnosis was subsequently confirmed by cardiac catheterization and angiography.

Case 7 This was a 39 year old housewife who came to observation because of progressively increasing exertional dyspnea. Pulse rate and blood pressure were normal. The heart was of normal size on percussion. There was a Grade 1/6 systolic murmur over the second left intercostal space and a wide fixed splitting of the second sound. In diastole a third sound was described. The x-ray showed right heart and pulmonary artery enlargement. The ECG showed right axis deviation and evidence of right ventricular hypertrophy.

The phonocardiogram confirmed that there was a fixed but narrow splitting of the second sound and a faint systolic murmur. It also demonstrated a mid diastolic murmur with presystolic accentuation (Fig. 7). The final diagnosis was atrial septal defect.

Cardiac catheterization performed in another hospital confirmed that there was an uncomplicated atrial shunt (secundum type).

Case 8 This patient was a 56 year old man with a history of chronic alcoholism and a recent onset of congestive failure. The heart was severely enlarged both to the right and the left on percussion and x-ray revealed that all chambers were enlarged. On auscultation a Grade 1 systolic murmur of high pitch and a low grade low pitched diastolic rumble were heard. The ECG was normal except for sinus tachycardia.

The phonocardiogram recorded in the low frequency range showed a prandistolic series of vibrations (Fig. 8). This was considered as a functional diastolic rumble.

Cardiac catheterization showed a moderate increase in the end diastolic pressure of both ventricles and no evidence of mitral stenosis. The final diagnosis was alcoholic cardiomyopathy.

Case 9 This patient was a 39 year old Negro man with a history of active pulmonary tuberculosis. Physical examination and chest films revealed active TB of the lungs with multiple infiltrates. The liver was palpable two fingerbreadths below the costal margin and was pulsatile. The jugular veins were distended and pulsatile. The heart was enlarged to both the right and the left. The first sound was faint, the second sound was loud. Both a Grade 2/6 prandistolic murmur and a Grade 2/6 middiastolic rumble were audible over the midprecordium with poor transmission to the apex. The ECG showed evidence of right ventricular hypertrophy and strain and tall T waves in Leads II, III and aVF. The ECG also showed a prolonged P-R interval (0.24 sec).

The apex phonocardiogram recorded in the low frequency range (not shown) revealed a large irregular complex in diastole (summation gallop). In the high frequency range (Fig. 9) it showed the prandistolic murmur and a middiastolic murmur well separated from both the previous second sound and the following first sound.

The jugular tracing showed an obvious wave of regurgitation (Fig. 9).

The conclusion was chronic cor pulmonale relative tricuspid insufficiency and functional diastolic murmur of the right heart.

Case 10 This 38 year old woman had a history of exertional dyspnea for several months. She had a pulse of 110 and a blood pressure of 106/78. Several episodes of severe sudden dyspnea with vague chest pain had occurred in the past and raised the question of multiple pulmonary embolizations. The apex was in the sixth left intercostal space 2 cm. to the left of the midclavicular line. The first sound was normal, the second sound was very loud at the left

sion of such criteria. This will be done below.

The phonocardiographic criteria are as follows:

1 *A wide area of recording of a diastolic murmur* or recording it in the second or third left intercostal space is in favor of a functional murmur. This fact can be explained by severe ventricular enlargement.

2 *Wide splitting of the second sound* is against mitral stenosis. Cor pulmonale, congenital shunts or severe right heart failure should be considered instead.

3 *High frequency of the murmur* (soft blowing murmur on auscultation) is unusual in mitral stenosis. In a special study devoted to this problem²² we found high frequency vibrations in only 12 per cent of the cases studied by phonocardiography.

4 *The murmur of mitral stenosis is frequently initiated by an opening snap.* This may be absent, however, in cases with very severe narrowing of the mitral valve often revealed by the finding of calcification on the x-ray. If there is no evidence of severe mitral stenosis (clinical, roentgenological or electrocardiographic data plus typical history) the lack of opening snap is against mitral stenosis. An opening snap can be found in exceptional cases of pure mitral insufficiency. It is usually followed by a very large third sound. Considering the various exceptions pro and con, a moderate importance should be given the lack of opening snap against mitral stenosis.

5 *High voltage of the murmur.* This is usually not appreciated by auscultation on account of the low frequency of the vibrations which are often close to or even below the threshold of the auditory system. In certain cases a barely audible murmur will appear in the tracing (with adequate filtration) as nearly as large or larger than the second sound. Cases of mitral stenosis with high voltage of the middiastolic murmur are extremely rare and are probably cases in which severe left ventricular damage due to concurrent processes adds a functional element to the organic murmur. High voltage is in favor of a functional rumble and against mitral stenosis.

6 *Wide separation of the murmur from the previous second sound.* The murmur of mitral stenosis starts with the beginning of

left ventricular filling, be this marked or not by an opening snap. A functional rumble usually starts later and its onset is very often marked by a large third sound. Thus the former starts generally from 60 to 120 msec after the aortic component of the second sound while the latter starts from 150 to 180 msec after such component. Late start of the middiastolic rumble is in favor of a functional rumble and against mitral stenosis.

7 *Middiastolic rumble without presystolic murmur in the presence of sinus rhythm.* While functional presystolic murmurs may occur, a functional diastolic rumble without presystolic accentuation is more common. In mitral stenosis with sinus rhythm if there is a middiastolic rumble there is usually also a presystolic murmur. Thus the presence of an isolated middiastolic rumble without atrial fibrillation should be considered at least as an atypical finding of mitral stenosis.

8 *Presystolic murmur that is not in crescendo.* In mitral stenosis with sinus rhythm the presystolic murmur is typically in crescendo. An exception is represented by patients with a very long conduction time. Functional murmurs in subjects with a normal P-R interval may have a sharp separation from the following first sound.

9 *Large third sound or fourth sound.* A patient with mitral stenosis nearly never has a large third sound. If there is a fourth sound at low frequency and a presystolic murmur at high frequency the stenosis is mild. A functional diastolic murmur starts very often with a large or even gigantic third sound. It may be followed by a fourth sound. Thus large diastolic sounds are usually evidence of a functional diastolic murmur.

10 *Effect of amyl nitrite inhalation.* This functional test very often increases the murmur of mitral stenosis by causing tachycardia. It has been stated that it would decrease the Austin Flint murmur²³ but we have found such a decrease only in some cases. Therefore it is difficult to assign a definite value to the results of this test.

Summary

The history of functional diastolic murmurs is reviewed. These murmurs are defined as murmurs not caused by valve ste-

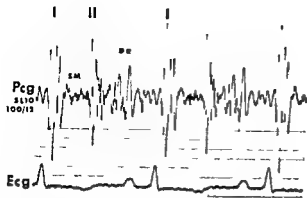


Fig. 10 Case 10—Mid-diastolic rumble (DR) of the right ventricle at apex in a 38 year old woman with chronic cor pulmonale

The final conclusion was coronary and hypertensive heart disease, possible papillary muscle dysfunction with mitral insufficiency, functional diastolic murmur related to left ventricular failure and possibly to ventricular dysrhythmia. The minimal aortic insufficiency considered is related to atherosclerosis; may have been an additional factor.

General considerations

The normal heart of a young person has already minimal, inaudible low frequency diastolic vibrations at the apex that can be recorded by means of adequate phonocardiographs.^{6,27} These vibrations may occasionally become larger and reach the threshold of audibility if there is an overactive cardiovascular system (from exercise after inhalation of amyl nitrite, hypermetabolic syndrome²⁸).

The cause of these vibrations can only be speculated upon. They are most likely arising in the left ventricular wall during its distension as suggested by the fact that they frequently start with a large third sound and represent after vibrations of this sound.

The murmur of mitral stenosis is caused by the difference in caliber between the mitral valve and the left ventricle. Thus it is related to eddies which start at the valve and spread from the inflow tract toward the apex. The vibrations of the blood are transmitted to the left ventricular wall and from this, to the chest wall.

Functional diastolic rumbles are usually encountered when one of the ventricles (most commonly the left, occasionally the right) is severely dilated when its filling is abnormally large (caused by valve insufficiency or shunts), when its pressure is high

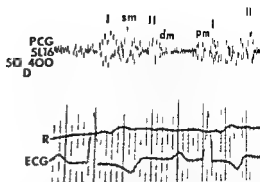


Fig. 11 Case 11—Diamond shaped systolic murmur early diastolic murmur and functional pre-systolic murmur (DM) in a 63 year old hypertensive man with coronary heart disease, left heart failure and Grade I A V block. There was also a minimal aortic insufficiency of an atherosclerotic nature.

(from hypertensive heart disease or cor pulmonale) and especially if the ventricular wall is damaged (from myocarditis or cardiomyopathy, coronary heart disease especially after infarcts, and even more if there is a ventricular aneurysm) or is in a state of failure.

The mechanism of these murmurs is still in question. More rapid and greater filling (from valve insufficiency or shunts) would increase the diastolic vibrations of the wall. High pressure would often alter the diastolic tension (from moderate to severe increase of the end diastolic pressure, often associated with strain or failure). Left ventricular damage from any cause would cause uneven compliance and uneven rapidity of filling of various sections of the left ventricle and this may be a cause of murmurs. Whether the old concept of 'relative mitral stenosis' (normal mitral opening, large ventricle) is still valid we do not know. Probably such a concept should be abandoned because the vibrations are usually found over a much larger area than in organic stenosis.

Differential diagnosis between functional diastolic murmurs and the murmur of mitral stenosis

Our experience in the study of functional diastolic murmurs dating from 1950¹⁸ led us to suggest certain differential data based on differences in phonocardiographic tracings.²⁰ The experience of the last 20 years indicates the need for a revision and extension.

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Julian Frieden

Medical treatment of angina pectoris III Pharmacology of sublingual nitrites as antianginal drugs

Wilbert S. Aronow, M.D.*
Long Beach and Irvine, Calif.

Coronary vasodilators have been advocated for the treatment of angina pectoris due to coronary artery disease. Although a coronary vasodilator drug might dilate collateral vessels, it is difficult to conceive of a drug producing vasodilatation in diseased sclerotic vessels in preference to more distensible vessels.¹ In fact, one should be concerned that angina might even be made worse in some patients by the vasodilator drug diverting blood from ischemic areas in the myocardium to other areas in which the vessels are capable of vasodilatation. Moreover, a drop in the systemic blood pressure induced by the vasodilator drug reduces the perfusion of the diseased sclerotic vessels. Hypoxia itself is also the best coronary vasodilator and maximum vasodilatation probably occurs during an attack of angina pectoris. Therefore, it is not surprising that vasodilator drugs have been found to be ineffective in the treatment of angina pectoris.^{2,3}

The mechanism of action of the nitrites in the relief of angina pectoris is not clearly established. Although sublingual nitroglycerin and other nitrites relax vascular

smooth muscle and produce coronary vasodilatation in normal man, these drugs do not increase coronary blood flow in patients with coronary artery disease at rest^{4,5} or during exercise.⁶ Moreover, the fall in systemic blood pressure induced by nitrites may, by decreasing coronary arterial perfusion pressure, actually decrease the myocardial oxygen supply.

Sublingual short acting nitrites such as nitroglycerin may be effective antianginal agents because they cause a decrease in the myocardial oxygen demand by the following mechanisms. Sublingual nitroglycerin reduces venous tone causing pooling of blood in the peripheral veins,⁷ and a decrease in cardiac output, stroke volume and ventricular volume.⁸ The fall in left ventricular end-diastolic pressure both at rest and during exercise after nitroglycerin in the absence of a change in left ventricular compliance also suggests a decrease in left ventricular volume.⁹ The reduction in the size of the heart by LaPlace's law decreases the intramural cardiac tension reducing the myocardial oxygen requirement. Sublingual nitroglycerin by causing arteriolar dilatation¹⁰ also

From the Cardiology Section, Medical Service, Long Beach Veterans Administration Hospital and the University of California College of Medicine, Irvine, Calif.
Received for publication April 3, 1972.

Reprint requests to Wilbert S. Aronow, M.D., Cardiology Section, Veterans Administration Medical Hospital, Long Beach, Calif. 90801.

*Staff Cardiologist and Chief of Pharmacology, Long Beach Veterans Administration Hospital, Associate Adjunct Professor of Medicine, University of California College of Medicine, Irvine, Calif.

nosis, though usually connected with severe changes of cardiovascular dynamics.

The phonocardiograms of 11 patients are presented and clinical and laboratory data of these patients are discussed. The mechanism of the functional diastolic murmurs is discussed, and differential phonocardiographic criteria are presented.

REFERENCES

- 1 Flint A. On cardiac murmurs. *Am J Med Sci* 44:29 1862
- 2 Steell G. The murmur of high pressure in the pulmonary artery. *Med Chron* 9:182 1888
- 3 Coombs C I. Rheumatic heart disease. New York 1924 W. Wood
- 4 White P D. Heart disease ed 4. New York 1951 The Macmillan Company
- 5 Blind L I, White P D and Jones T D. The development of mitral stenosis in young people with a discussion of the frequent misinterpretation of a mid diastolic murmur at the cardiac apex. *Am Heart J* 10:995 1935
- 6 Bramwell C. Signs simulating those of mitral stenosis. *Brit Heart J* 5:24 1943
- 7 Gibson S. Eyes, hands and ears in the diagnosis of heart disease in children. *Pediatr Clin North Am* 1:3 1954
- 8 Weinstein W and Lev M. Apical diastolic murmurs without mitral stenosis. *Am Heart J* 23:809 1942
- 9 Ravin A and Darley W. Apical diastolic murmurs in patent ductus arteriosus. *Ann Intern Med* 33:903 1950
- 10 Ishikawa B L and Medrano G A. Retumbo apical en la persistencia del conducto arterial. *Arch Inst Cardiol Mex* 32:430 1962
- 11 Likoff W, Geckeler G D and Gregory J E. Function of mitral stenosis produced by an intra-atrial tumor. *Am Heart J* 47:619 1954
- 12 Bleifer S, Dick S, Goshman A and Donoso E. The auscultatory and phonocardiographic findings in mitral regurgitation. *Am J Cardiol* 5:191 1960
- 13 Nixon I G F, Wooler G H and Radigan L R. The opening snap in mitral incompetence. *Br Heart J* 22:395 1960
- 14 Nixon P G F. The third heart sound in mitral regurgitation. *Br Heart J* 23:677 1961
- 15 Perloff J K and Harvey W P. Auscultatory and phonocardiographic studies of pure mitral insufficiency. *Progr Cardiovasc Dis* 5:17 1962
- 16 Bloemer H, Klinger W and Kolb P. Der Mitraloffnungston bei der Mitral inuffizienz. *Kreislaufforsch* 50:888 1961
- 17 Lusada A A. Heart. Baltimore 1949 and 1954 The Williams & Wilkins Company
- 18 Lusada A A and Perez Montes L. A phonocardiographic study of apical diastolic murmurs simulating those of mitral stenosis. *Ann Intern Med* 33:36 1950
- 19 Lusada A A. The heart beat. New York 1953 Paul B. Hoeber Inc.
- 20 Lusada A A and Harring O M and Zilli A B. Apical diastolic murmurs simulating mitral stenosis II. Graphic differentiation. *Ann Intern Med* 42:644 1955
- 21 Lusada A A, Szatkowski J, Testelli M and Bendezu Prieto J. Apical diastolic and presystolic murmurs of proved functional nature. *Am J Cardiol* 4:501 1959
- 22 Lusada A A and Zilli A B. The phonocardiogram in rheumatic fever and rheumatic heart disease. In Lusada A A, editor. *Cardiology: An encyclopedia of the cardiovascular system* vol III part 7. New York 1959 Blakiston Division McGraw Hill Book Company
- 23 Lusada A A. From auscultation to phonocardiography. St. Louis 1965 The C. V. Mosby Company
- 24 Liebman J and Saad S. Diastolic murmurs in apparently normal children. *Circulation* 28:755 1968
- 25 Argano B and Lusada A A. Innocent diastolic murmurs. *Chest* 59:443 1971
- 26 Farinelli A, Zanardi F, Alvisi V and Sbrighi V. Rilevi poliocardiografici su di un fenomeno vibratorio mesodiastolico rilevabile in cuori giovanili. *Minerva Med* 57:3369 1966
- 27 Lusada A A. The sounds of the normal heart. St. Louis 1972 W. Green
- 28 Mehta S and Lusada A A. High pitched murmur in mitral stenosis. *Indian Heart J* 18:320 1966
- 29 Kager R G. Differentiation of Austin Flint murmur and mitral stenosis murmurs by amyl nitrite. *Clin Res* 11:24 1963 (Abst.)
- 30 Lusada A A. The sounds of the diseased heart. St. Louis W. Green. In press

REFERENCES

1. Powe G C. Coronary vasodilator therapy for angina pectoris. *Am HEART J* 69: 691 1964
2. Lieb S and DeGriff A C. Coronary vasodilator. *Dis. Chest* 44: 533 1963
3. DeGriff A C and Lyon A F. Evaluation of dipyridamole (Persantin). *Am HEART J* 69: 173 1963
4. Gorlin R, Brachfeld A, MacLeod C, and Bopp P. Effect of nitroglycerin on the coronary circulation in patients with coronary artery disease or increased left ventricular work. *Circulation* 19: 103 1959
5. Bernstein L, Friesinger G C, Lichtlen P J, and Ross R. S. The effect of nitroglycerin on the systemic and coronary circulation in man and dogs. Myocardial blood flow measured with xenon. *Circulation* 33: 107 1966
6. Parker J O, West R. I, and Di Giorgi S. The effect of nitroglycerin on coronary blood flow and the hemodynamic response to exercise in coronary artery disease. *Am J Cardiol* 25: 59 1971
7. Powe G C, Chelius C J, Afonso S, Gurtner H P, and Crumpton C W. Systemic and coronary hemodynamic effects of erythrol tetranitrate. *J Clin. Invest* 40: 1217 1961
8. Mason D T and Braunwald I. The effects of nitroglycerin and amyl nitrite on arteriolar and venous tone in the human forearm. *Circulation* 32: 311 1965
9. Williams J J Jr, Fleck E, and Braunwald L. Studies in cardiac dimensions in intact unanesthetized man. V. Effects of nitroglycerin. *Circulation* 32: 67 1965
10. Goldstein I I, Rowing D R, Redwood D H, Beler G D, and Laitin S E. Clinical and circulatory effects of isosorbide dinitrate. *Circulation* 43: 69 1971
11. Aronow W S and Chesluk H M. Sublingual isosorbide dinitrate therapy versus sublingual placebo in angina pectoris. *Circulation* 41: 869 1970
12. Horwitz L D, Gorlin R, Taylor W J, and Kemp H G. Effects of nitroglycerin on regional myocardial blood flow in coronary artery disease. *J Clin Invest* 50: 1518 1971
13. Wang J, Arthur V S, and Meiser J V. Nitroglycerine induced flow maldistribution in coronary stenosis. *Circulation* 44(Suppl. 11): 59 1971
14. Kinsella D, Troup W, and McGregor M. Studies with a new coronary vasodilator drug Persantin. *Am HEART J* 69: 146 1965

lowers the arterial pressure. By reducing systolic intraventricular pressure and the resistance to ventricular ejection, the myocardial oxygen demand is further decreased. A reduction in the arterial pressure, cardiac output, and stroke volume causes a decrease in external work performed by the left ventricle, leading to a reduction in myocardial oxygen consumption.

However, nitroglycerin also increases the resting heart rate and the tension-time index was not significantly altered by nitroglycerin in patients with angina pectoris at rest and during exercise compared to the control periods.⁶ A significant increase in systolic ejection rate despite a lower level of left ventricular end diastolic pressure and volume also suggests that myocardial contractility was probably increased during exercise after nitroglycerin.⁶ This increase in myocardial contractility increases the myocardial oxygen requirement.

Goldstein and his associates¹⁰ reported that in patients with angina pectoris due to coronary artery disease who performed upright exercise sublingual isosorbide dinitrate tested as a short acting nitrate produced lower systolic and mean blood pressures, a faster heart rate, a shorter ejection time and a slightly reduced overall heart size. Sublingual nitroglycerin and sublingual isosorbide dinitrate produced very similar alterations in the circulatory response to upright exercise in their patients with angina pectoris. The duration of action of sublingual isosorbide dinitrate was also similar to that of sublingual nitroglycerin in their patients with angina.

We reported¹¹ that in patients with angina pectoris due to coronary artery disease who performed upright exercise one hour after administration of sublingual medication there was no significant difference in the groups' mean systolic or diastolic blood pressure, heart rate or product of systolic blood pressure and heart rate at rest or immediately after exercise induced angina during treatment of sublingual isosorbide dinitrate compared to sublingual placebo. Goldstein and his associates¹⁰ data and our data provide hemodynamic evidence for the ineffective-ness^{10, 11} of sublingual isosorbide dinitrate as a long acting antianginal agent.

Horowitz and his co-workers¹² found that

sublingual nitroglycerin induced a significant increase in coronary blood flow to diseased regions in patients with angina pectoris due to coronary artery disease.

These investigators concluded that sublingual nitroglycerin is efficacious as an antianginal agent partially because it causes redistribution of coronary blood flow so that a greater portion of the total coronary blood flow is delivered to ischemic regions, in addition to its ability to decrease myocardial oxygen demand. However, Wing and his associates¹³ reported that a constant infusion of nitroglycerin, while increasing total coronary blood flow, decreased left anterior descending coronary arterial flow in 7 of 12 dogs (58 per cent) with a stenosed left anterior descending coronary artery, did not change left anterior descending flow in 3 of these 12 dogs (25 per cent), and increased left anterior descending flow in only 2 of the 12 dogs (17 per cent).

Dipyridamole has been demonstrated to be a powerful coronary vasodilator.¹⁴ However, unlike short acting nitrates such as nitroglycerin, dipyridamole does not reduce the myocardial oxygen demand in patients with coronary artery disease. Dipyridamole has also been shown in several double blind studies to be no more effective than placebo in the treatment of angina pectoris due to coronary artery disease.^{15, 16} There is no good clinical evidence documenting that any antianginal drug is effective because it is a coronary vasodilator.

In summary, coronary vasodilators do not increase coronary blood flow in patients with coronary artery disease nor reduce myocardial oxygen demand. Although sublingual short acting nitrates such as nitroglycerin do not increase the oxygen supply to the myocardium, they may be effective as antianginal agents due to a reduction in myocardial oxygen requirement. This decrease in myocardial oxygen demand is primarily caused by peripheral vasodilatation causing a reduction in left ventricular volume. Long acting nitrates and other coronary vasodilators do not appear either to increase the oxygen supply to the myocardium or to decrease the myocardial oxygen demand and therefore are ineffective as antianginal agents.

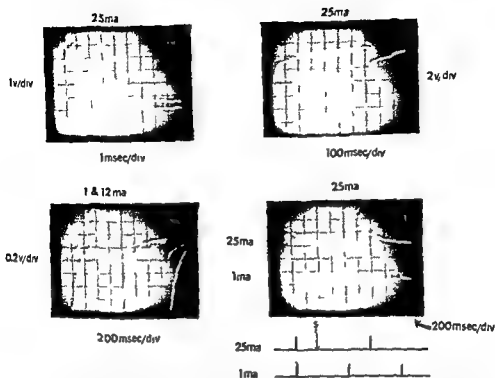


Fig. 1 Voltage wave forms of the 5840 Medtronic demand pacemaker connected to a USC1 catheter with electrodes 1 cm. apart. All measurements were recorded with the catheter in normal saline without additional resistance. The upper panel on the left shows the duration of the pacemaker impulse at 1.6 msec and the presence of a relatively large time constant voltage after the initial impulse. The upper panel on the right also shows the after potential between the pacemaker impulses. The lower panel on the left shows the varying contribution of the after potential according to the energy settings on the pacemaker. The pacemaker rates are identical at 1 and 12 mA and the initial pulses with both settings are superimposed at the lower end of the photograph. Note that the pacemaker after potential belonging to the 12 mA discharge (on the right of the photograph) with the 1 mA setting contains a sharper di/dt segment outside the refractory period of 30 msec. The lower panel on the right shows the double reset phenomenon at 25 mA. The signal provided by the after potential recycles the pacemaker with one full escape interval ($\phi = \text{volt/div} \times \text{div}/\text{ion}$).

REFERENCES

- 1 Beller W M and Pupillo C. Potentially dangerous rate and amplitude control interaction on an external battery powered demand pacemaker. *Am HEART J* 81:717 1971
- 2 Barold S S and Girdula J J. Evaluation of normal and abnormal sensing function of demand pacemaker. *Am J Cardiol* 28:701 1971
- 3 Barold S S. Clinical significance of pacemaker

refractory periods (editorial). *Am J Cardiol* 28:737 1971

- 4 Cheatham J E. Medtronic Inc. Personal communication 1971
- 5 Keller J W, Gosselin A J, Nathan D A, Stults R H, Bhavani S and Lister J. Rhythmic anomalies in contemporary demand pacing. *Am J Cardiol* (in press)
- 6 Medtronic New. Vol II issue 7 p 1 1970

Reflex vasodilatation and Raynaud's disease

As the writer has already noted, it is not clear that there is a drug available that specifically dilates the vessels of the fingertips. Vasodilator drugs dilate most or all blood vessels of the body. Such a vasodilator could readily shift blood from the fingertips to the

large vascular reservoir of the body, conceivably resulting in a paradoxical therapeutic response. To produce significant dilatation of the digital vessels the patient needs only to keep the body warm to the point of sweating by wearing coats, sweaters, gloves

Annotations

"Double reset" of demand pacemakers

Beller and Pupillo recently documented the unusual behavior of the 5840 Medtronic demand pacemaker when used at energy levels over 12 mA with a particular USCI catheter.¹ They observed in this situation intermittent slowing of the pacemaker rate and suggested that the abnormality was related to the demand function since the pacemaker rate remained constant during fixed rate pacing.

This disturbance has been and remains a potential problem in the design of all demand pacemakers. When a pacemaker delivers a 1 or 2 msec stimulus it charges the electrode tissue interface to a large DC potential.² Dissipation of this large voltage (generally over 1000 mV) between pacemaker pulses creates a time changing voltage (pacemaker after potential) that may be sensed by the pacemaker as it comes out of its refractory period.^{3,4} (Fig. 1)

The electrocardiograms in Beller and Pupillo's paper show in strips A to E ventricular pacing by a 5840 Medtronic pacemaker with an automatic interval of approximately 640 msec. In strip I during pacing at 12 mA the interval between consecutive pacemaker impulses lengthened intermittently to a constant value of 940 to 960 msec. Thus the pacemaker appeared to sense a signal 300 to 320 msec after the pacemaker stimulus or about 50 to 70 msec after its delivery refractory period which usually lasts 250 msec in this particular model.⁵ This is consistent with sensing the pacemaker after potential just outside the delivery refractory period.^{6,7} Since for this pacemaker the true escape interval equals the automatic interval the 50 to 70 msec delay represents the time required for the voltage decay wave form to activate the demand mechanism and may also reflect intrinsic delays in the circuit according to the polarity of the incoming signal.⁸

The manufacturers have alerted the medical profession of this particular problem and offered to modify the pacemakers to eliminate this characteristic.⁹ Although the manufacturers suggested that this phenomenon could be compensated for by adjusting the rate dial until the required rate was achieved,⁹ we feel that this approach is sometimes unsatisfactory for the following reasons: (1) The disturbance is often intermittent. Thus adjustment of the pacemaker rate during continuous over sensing of the pacemaker after potential may lead to undesirable rapid pacing rates when the pacemaker after potential can no longer provide an adequate signal to suppress the pacemaker. (2) Recycling of this particular pacemaker at the end of its delivery refractory period doubles its effective refractory period to about 500 msec since its sensing and delivery refractory periods are equal.³ This relatively long refractory period may lead to spontaneous

beats being unsensed by the pacemaker a complication we have actually observed.

We have never considered the double reset characteristic of the 5840 Medtronic pacemaker potentially dangerous as did Beller and Pupillo probably because we have always been able to deal with it. The frequent intermittency of the disturbance over 12 mA implies that the signal is marginal and often incapable of being sensed. Therefore we have always corrected the problem by a slight reduction of the input sensitivity of the pacemaker (middle dial) provided the voltage of the ventricular electrogram is well above 2 mV. When the QRS signal is relatively low we would not recommend reduction of the input sensitivity.

We have observed as did Beller and Pupillo the double reset phenomenon with USCI pacing catheters with electrodes 1 cm apart but have seen it occasionally when the electrodes are 2 cm apart and also with the new Medtronic 5 French 6/00 catheter with electrodes 2.8 cm apart. Many examples of apparent sensing of the T wave of paced ventricular beats may indeed represent sensing of the after potential with or without the addition of T wave voltage.

The double reset problem from sensing the pacemaker after potential has not been restricted to Medtronic pacemakers and has been observed to occur with demand pacemakers from several other manufacturers.⁹ The approach to solving this problem constitutes important considerations in the design of demand pacemakers and includes: (1) using appropriate pacing catheters such as the Medtronic 5821 with a 5840 pacemaker to avoid the larger circuit capacitance when unsuitable catheters are used (a larger capacitance will be less completely discharged during the refractory period and thus more prone to generate a significant signal outside the refractory period); (2) better low frequency rejection circuitry; (3) reduction of the pacemaker sensitivity easily accomplished manually on the external units; (4) increasing the delivery refractory period so that it will contain the large dv/dt segment of the after potential; (5) changing the output time constant of the pacemaker electrode system so that the after potential discharge occurs faster.

S. Serge Barold, M.D., M.R.I.C.P.
Director of Cardiology
Michael Carroll
Cardiology Technologist
Highland Hospital
South 1st and Bellevue Dr.
Rochester, N.Y. 14620

*Pre-entitled to The General Hospital & Heart Review
1407

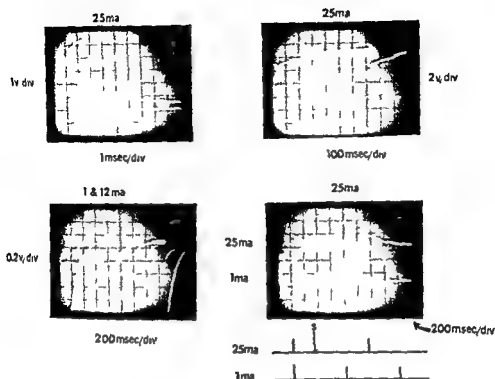


Fig 1 Voltage wave forms of the 5840 Medtronic demand pacemaker connected to a USC1 catheter with electrode 1 cm apart. All measurements were recorded with the catheter in normal saline without additional resistive load. The upper panel on the left shows the duration of the pacemaker impulse at 1.6 msec and the presence of a relatively large time changing voltage after the initial impulse. The upper panel on the right also shows the after potential between the pacemaker impulses. The lower panel on the left shows the varying configurations of the after potential according to the energy settings on the pacemaker. The pacemaker rates are identical at 1 and 12 mA and the initial pulses with both settings are superimposed at the lower end of the photograph. Note that the pacemaker after potential belonging to the 1.9 mA discharge (on the right of the trace corresponding with the 1 mA setting) contain a sharper dv/dt segment outside the refractory period of 250 msec. The lower panel on the right shows the double re-set phenomenon at 25 mA. The signal provided by the after potential recycles the pacemaker with one full escape interval ($v = \text{volt/div} = \text{division}$).

REFERENCES

1. Beller B M and Pupillo C. Potentially dangerous rate and amplitude control interaction in external battery powered demand pacemaker. *Am HEART J* 81:717 1971.
2. Barold S S and Gidula J J. Evaluation of normal and abnormal sensor function of demand pacemakers. *Am J Cardiol* 28:201 1971.
3. Barold S S. Clinical significance of pacemaker refractory periods (editorial). *Am J Cardiol* 28:737 1971.
4. Cheatham J E. Medtronic Inc. Personal communication 1971.
5. Keller J W, Gosselin A J, Nathan D A, Stult R H, Bhavani S and Lister J. Rhythm anomalies in contemporary demand pacing. *Am J Cardiol* (In press).
6. Medtronic News Vol II issue 2 p 1 1970.

Reflex vasodilatation and Raynaud's disease

As the writer sits in an electric chair there is no doubt that he perfectly dilates the vessels of the fingertips. Vasodilation of late most of the blood vessels of the body. Such a vasodilatation could readily shift blood from the fingertips to the

larger vascular reservoirs of the body conceivably resulting in a paradoxical therapeutic response. To produce significant dilatation of the digital vessels the patient needs only to keep the body warm to the point of sweating by wearing coats sweaters gloves

"Double reset" of demand pacemakers

Beller and Pupillo recently documented the unusual behavior of the 5840 Medtronic demand pacemaker when used at energy levels over 12 mA with a particular USC1 catheter.¹ They observed in this situation intermittent slowing of the pacemaker rate and suggested that the abnormality was related to the demand function since the pacemaker rate remained constant during fixed rate pacing.

This disturbance has been and remains a potential problem in the design of all demand pacemakers. When a pacemaker delivers a 1 or 2 msec stimulus it charges the electrode tissue interface to a large DC potential.² Dissipation of this large voltage (generally over 1000 mV) between pacemaker pulse creates a time changing voltage (pacemaker after potential) that may be sensed by the pacemaker as it comes out of its refractory period.³ (Fig 1)

The electrocardiograms in Beller and Pupillo's paper show in strips A to C ventricular pacing by a 5840 Medtronic pacemaker with an automatic interval of approximately 640 msec. In strip 1 during pacing at 12 mA the interval between consecutive pacemaker impulses lengthened intermittently to a constant value of 940 to 960 msec. Thus the pacemaker appeared to sense a signal 300 to 320 msec after the pacemaker stimulus or about 50 to 70 msec after its delivery refractory period which usually lasts 250 msec in this particular model.² This is consistent with sensing the pacemaker after potential just outside the delivery refractory period.³ Since for this pacemaker the true escape interval equals the automatic interval the 50 to 70 msec delay represents the time required for the voltage decay wave form to activate the demand mechanism and may also reflect intrinsic delays in the circuit according to the polarity of the incoming signal.²

The manufacturers have alerted the medical profession of this particular problem and offered to modify the pacemakers to eliminate this characteristic.⁴ Although the manufacturers suggested that this phenomenon could be compensated for by adjusting the rate dial until the required rate was achieved,⁴ we feel that this approach is sometimes unsatisfactory for the following reasons: (1) The disturbance is often intermittent. Thus adjustment of the pacemaker rate during continuous over sensing of the pacemaker after potential may lead to undesirable rapid pacing rates when the pacemaker after potential can no longer provide an adequate signal to suppress the pacemaker. (2) Recalling of this particular pacemaker at the end of its delivery refractory period doubles its effective refractory period to about 500 msec since its sensing and delivery refractory periods are equal.² This relatively long refractory period may lead to spontaneous

beats being unsensed by the pacemaker a complication we have actually observed.

We have never considered the double reset characteristic of the 5840 Medtronic pacemaker potentially dangerous as did Beller and Pupillo, probably because we have always been able to deal with it. The frequent intermittency of the disturbance over 12 mA implies that the signal is marginal and often incapable of being sensed. Therefore, we have always corrected the problem by a slight reduction of the input sensitivity of the pacemaker (middle dial) provided the voltage of the ventricular electrogram is well above 2 mV. When the QRS signal is relatively low we would not recommend reduction of the input sensitivity.

We have observed as did Beller and Pupillo the double reset phenomenon with USC1 pacemaker catheters with electrodes 1 cm apart but have seen it occasionally when the electrodes are 2 cm apart and also with the new Medtronic 5 French 6100 catheter with electrodes 2.8 cm apart. Many examples of apparent sensing of the T wave of paced ventricular beats may indeed represent sensing of the after potential with or without the addition of T wave voltage.

The double reset problem from sensing the pacemaker after potential has not been restricted to Medtronic pacemakers and has been observed to occur with demand pacemakers from several other manufacturers.⁵ The approach to solving this problem constitutes important considerations in the design of demand pacemakers and includes: (1) use of appropriate pacing catheters such as the Medtronic 5821 with a 5840 pacemaker to avoid the larger circuit capacitance when unsuitable catheters are used (a larger capacitance will be a completely discharged during the refractory period and thus more prone to generate a significant signal outside the refractory period); (2) better low frequency rejection circuitry; (3) reduction of the pacemaker sensitivity easily accomplished manually on the external units; (4) increasing the delivery refractory period so that it will contain the large dv/dt segment of the after potential; (5) changing the output time constant of the pacemaker electrode system so that the after potential discharge occurs faster.

S. Serge Barold, M.D., M.R.I.C.P.
Director of Cardiac
Michael Corbett
Cardiology Technical
Highland Hospital
South Ave. and Bellevue Dr.
Rochester, N.Y. 14601

Assessment of LVEDP from right heart pressures during atrial pacing

Recent reports have described the use of right atrial pacing through a pacing induced change in left ventricular end-diastolic pressure (LVEDP) and stroke work to determine left ventricular function in patients with coronary artery disease.^{1,2} When pulmonary vascular resistance is normal a good correlation frequently exists between pulmonary artery end-diastolic pressure, pulmonary wedge pressure, or mean pressure and the LVEDP.^{3,4} If this relationship held true during atrial pacing, then pulmonary artery and wedge pressures could be used to estimate LVEDP and in association with systemic arterial pressures and cardiac output, LV function curves could be determined easily in the coronary care unit. This would be a natural extension of the hemodynamic studies which are being used presently in the early evaluation of the patient following myocardial infarction⁵ and would eliminate the need to obtain left heart pressures.

In order to evaluate this possibility, simultaneous right heart and left ventricular end-diastolic pressures were recorded in patients with coronary artery disease during atrial pacing studies as previously described.⁶ Table 1 discloses that at a control heart rate of 81 ± 3 beats per minute, pulmonary artery end-diastolic and wedge pressures gave a fairly accurate estimate of LVEDP. However, as heart rate was gradually increased by atrial pacing to an average of 130 ± 6 beats per minute, right heart pressures changed insignificantly while LVEDP declined a linear fashion. Therefore, significant differences existed between these right heart pressures and LVEDP and at pacing rates over 100 they could not be used to estimate LVEDP. With the interruption of pacing, the right heart and left ventricular end-diastolic pressures resumed their correlation within one to two beats. This lack of correlation at rapid rates is probably related to the increase in PR interval with atrial pacing (Table 1) and a superimposition of the A and V waves in the left atrial and consequently the wedge pressures.⁷ It is probable that this divergence of right heart and LV end-diastolic pressures would also occur during any

spontaneous atrial tachycardia with prolonged intervals and certainly would be present when atrial pacing is employed to suppress ventricular arrhythmias.⁸ Therefore, under these circumstances as well as in an attempt to determine myocardial function, left heart pressures must be measured.

Joseph W. Linhart, M.D.
Director, Division of Cardiology
Hahnemann Medical College and Hospital
730 N. Broad St.
Philadelphia, Pa. 19101

REFERENCES

1. Linhart J W. Myocardial function in coronary artery disease determined by atrial pacing. *Circulation* 44: 703, 1971.
2. Parker J O, Khaja F and Case R B. Analysis of left ventricular function by atrial pacing. *Circulation* 43: 741, 1971.
3. Falcov R E and Resnekov L. Relationship of the pulmonary artery end-diastolic pressure to the left ventricular end-diastolic and mean filling pressures in patients with and without left ventricular dysfunction. *Circulation* 42: 64, 1970.
4. Jenkins R S, Bradley R D and Branthwaite M A. Evaluation of pulmonary artery end-diastolic pressure as an indirect estimate of left atrial mean pressure. *Circulation* 42: 75, 1970.
5. Schoenfeldt H, Filmore S, Scheidt S and Kullip T. Estimation of left ventricular diastolic pressure from pulmonary artery pressure in acute myocardial infarction. *Circulation* 42(11): 59, 1970 (Abstr.).
6. Ramo B W, Myers N, Wallace A G, Starmer F, Clark D O and Whalen R E. Hemodynamic findings in 123 patients with acute myocardial infarction on admission. *Circulation* 42: 567, 1970.
7. Fluck D C, Valentine P A, Trester B, Higg B, Reid D, Steiner R E and Mounsey J P D. Right heart pressures in

Table 1 Hemodynamics during atrial pacing

	HR	PR	PAW	PAW 1	LVEDP(1)	PAEDP	LVEDP(2)
Control	81 ± 3	0.16 ± 0.01	11 ± 2	10 ± 4	12 ± 2	14 ± 2	13 ± 3
Pacing	130 ± 6	0.22 ± 0.01	13 ± 2	17 ± 3	6 ± 2	18 ± 3	9 ± 2

HR = heart rate (beats per min); PR = PR interval (sec); PAW = pulmonary artery wedge pressure; LVEDP = left ventricular end-diastolic pressure; PAEDP = pulmonary artery end-diastolic pressure; All values are standard error of the mean; \dagger indicates difference (< 0.05) between LVEDP and PAW, PAW A, and PAEDP during pacing; \ddagger all values significantly different; LVEDP during pacing and PAW A may be compared to LVEDP(1) and PAEDP to LVEDP(2).

5/20/69

54 WF



6/24/69



9/3/69



Fig. 1 Raynaud's disease of the fingertips in a 54 year old Caucasian woman who was suffering excruciating digital pain. The ischemic and necrotic tissue healed nicely merely by keeping the body, hands and feet warm at all times with warm clothing and loose fleece lined or woolen gloves. The practice of keeping the body warm is being continued; the lesions remain healed and the patient is symptom free.

woolen stockings, mufflers and other warm clothes and warm bed clothing according to the environmental conditions. It is well known that when the body tends to become too warm there is a fairly intense vasodilatation of all blood vessels of the hand, feet, fingers and toes in an effort to lose body heat. The patient must avoid touching cold things, exposing himself to cool or cold drafts, getting wet or doing anything which would result in constriction of the digital vessels. Vibrations, excessive washing

3/15/67

38 WF



1/30/68



Fig. 2 Raynaud's disease of the fingertips in a 38 year old Caucasian woman who was suffering excruciating digital pain. The ischemic and necrotic tissue healed following reflex digital vasodilatation produced by keeping the body and extremities warm with proper clothing and use of loose warm gloves. Body warmth is being continued; the lesions remain healed and the patient is free from symptoms.

of the hands, use of the fingers and other forms of even mild trauma must of course receive serious consideration in therapy.

Figs. 1 and 2 show the results of management of digital disease with reflex digital vasodilatation produced by body and extremity warmth achieved merely by the use of warm clothing. No vasodilator drugs were used in these cases. The digital vasodilatation is produced reflexively on a continuous basis simply by keeping the body warm. The two patients under consideration continue to do well after two and four years respectively previous to the periods shown; their disease was rapidly worsening in spite of treatment with vasodilator drugs. It is unnecessary to point out that an intact sympathetic nervous system is necessary for the production of reflex vasodilatation.

George E. Burch, M.D.
Department of Medicine
Tulane University School of Medicine
1450 Tulane Ave.
New Orleans, La. 70119

REFERENCES

1. Burch, G. L., Cole, J. H., and Miller, G. C. Reflex vasodilatation in the treatment of peripheral vascular disease. *Am. Heart J.* 77:719, 1969.

waveform correction which must have required nothing more than drafting board, T-square, right angle triangle and divider or compass—almost Euclidean in its constructional simplicity! In Einthoven's method the coordinates of successive points on the electrometer curve were carefully measured and the first derivative of the curve was approximated as the slope of straight lines connecting adjacent pairs of points.⁴ His treatment of electrometer records revealed the presence of such common place but previously obscured ECG features as the Q and S waves. This tantalizing glimpse of the future must have served as a powerful stimulus in his efforts to devise a dynamically adequate recorder for the string galvanometer.

Combining very old and quite modern instrumentation to either in a curious mix we recently retraced some of the steps which Einthoven took in his pursuit of waveform correction. We photographically magnified several fold the published Lead I electrometer record of his subject "Mr. V. d. W."⁴ and taped the enlarged curve to the drum of a computer-driven incremental plotter. A home made optical scanner was mounted in the pen carriage of the plotter. Under program control the scanner traced out the electrometer curve, storing the digitized values of deflection in computer memory. The curve corresponding to the first time derivative was determined by numerical differentiation and added to the original curve in an amount sufficient to construct an ECG complex with about the same R/T amplitude ratio which Einthoven achieved in his own treatment of the same material. A cut and try approach was necessary since the decay constant of the electrometer was not stated in the source publication. The numerical equivalent of a high frequency rolloff filter was applied to smooth out the fine notches and discontinuities which are produced by the differentiation of discretized and somewhat grainy data. The original curve taken from Einthoven's paper together with the results of our numerical processing are illustrated in Fig. 1.

Our reconstructed curve differs in some respects from that obtained by Einthoven. For example we find our P wave to be less crisply defined than his. The Q deflection is somewhat less prominent, and the S more prominent. Since the principle of waveform correction is so straightforward and simple of application, we surmise that the differences in results are probably due to some distortion of his original curve in the cut which was prepared for publication. Regardless of what the explanation may be, the important outcome of our vicarious experience was the restoration of peak R and T amplitudes to an approximately correct relation and the retrieval of the Q and S deflections from the dynamic morass of the sluggish mercury column.

The valiant pioneering attempts by Burch and Einthoven to achieve records of good dynamic quality were remarkable because of the rudimentary instrumentation available for the task. Their work implicitly emphasizes the need for both technical techniques and a full appreciation of the pertinent principles of instrumentation for accurate physiological recording, as to be achieved. We should hope that these lessons from the past would be reflected fully more than three quarters of a century later

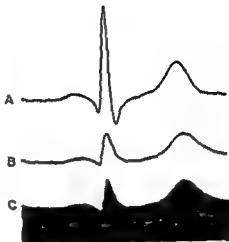


Fig. 1 Application of modern signal processing techniques to waveform correction of an electrocardiographic complex recorded by Lippmann's capillary electrometer. The lower curve (C) is an electrometer recorded Lead I tracing taken from a publication of Einthoven's. The middle curve (B) shows a computer produced replica of the original (C) converted to digitized form by an optical scanner and drawn to identical scale by an incremental plotter. In the upper curve (A) the numerical corrective measures described by Einthoven and G. J. Burch have been employed to recover some of the more rapid signal variations which were obscured by the sluggish dynamic properties of the capillary electrometer. Further discussion in text.

in the quality of record which we demand of ourselves in modern electrocardiographic practice.

Daniel A. Brady
John W. Cox Jr.
Harry J. Phillips
Francis W. Keller
Division of Clinical Physiology
University of Tennessee Medical Units
Memphis Tenn 38103

REFERENCES

1. Waller A. D. On the electromotive changes with the beat of the mammalian heart and of the human heart in particular. Phil Trans R. Soc London 180B 169 1889.
2. Einthoven W. Lippmann's Capillar Elektrometer zur Messung schnell wechselnder Potentialunterschiede. Arch Ges Physiol 26 528 1894.
3. Burch G. J. On a method of determining the value of rapid variations of a difference of potential by means of the capillary electrometer. Proc. I. Soc. Lond 18 89 1890.
4. Einthoven W. Die galvanische Registrierung des menschlichen Elektrokardiogramms zugleich eine Beschreibung der Anwendung des Capillar Elektrometers in der Physiologie. Arch Ges Physiol 99 472 1903.

- acute myocardial infarction *Br Heart J* 20:48 1967
- 8 Fister J W, Stem I, Kowalsky H D, Linn S H and Dumito A N. Atrioventricular conduction in man. Effect of rate exercise isoproterenol and atropine on the PR interval *Am J Cardiol* 16:516 1965

- 9 Leighton R I, Zaron S J, Robinson J W and Weisser A M. Effects of atrial pacing on left ventricular performance in patients with heart disease *Circulation* 30:615 1969
- 10 Sowton I, Leatham A and Carson P. The suppression of arrhythmias by artificial pacemaking *Lancet* 2:1039 1964

Einthoven, G. J. Burch, and the capillary electrometer

Human electrocardiography is a venerable art and science. Records on human beings were first published by Waller¹ in 1889. Two years earlier he had published records obtained by applying electrode directly to the exposed rabbit heart. Scientific writing being the disproportionate exercise that it is, one can only guess the sense of excitement that Waller must have felt when he finally succeeded in recording electrical impulses from an intact subject.

At that time, and for more than the next decade, the electrocardiogram (ECG) was recorded by means of Hippinimus's capillary electrometer. The electroactive element in this device consisted of a mercury-sulfuric acid interface in a vertically mounted glass capillary. Application of an electrical potential difference across the phase boundary changed surface tension by a small amount and thus caused microscopic movement of the mercury meniscus. Casting a highly magnified shadow of the meniscus on a laterally moving light-sensitive plate produced a graphic record of the electrical event. Waller's original records are rather indistinct due partly to low signal amplitude and partly to poor photographic contrast between the mercury and sulfuric acid phases. This situation improved as techniques developed. The capillary electrometer records eventually obtained by Einthoven show relatively adequate signal amplitude and are marvels of photographic clarity.

The capillary electrometer was the only device available at the time which could even begin to follow the rapid deflections of the cardiac signal and other electrophysiologic events having similar rates of change. Even so, it was not fully equal to the task of faithful ECG registration. With its large viscous drag due to movement of fluid through a capillary tube and the low ratio of recoil force to mass it could not help but be a sluggish heavily overdamped instrument. Indeed viscous drag so greatly dominated the dynamic picture that mass could be disregarded in applying the usual differential equations of motion. As a result abrupt application of a constant potential difference fell far short of producing the steplike change which one would expect of a dynamically adequate instrument instead in accordance with theoretical prediction movement of the meniscus traced rather slowly an exponential decay curve in arriving at its new level.

These facts were well known to Einthoven² and equally so to C. J. Burch³ who worked on the electrical activity of frog skeletal muscle in the Physiological Laboratory at Oxford. Both men fully recognized that appreciable amounts of waveform information were being wiped out or buried by the sluggish response of the capillary electrometer and both sought means for restoring the blurred details of signal configuration. Einthoven's work appears to have been the more analytical, at least to the extent that mathematical formulations were spelled out in detail. On the other hand, the underlying dynamic principles were implicit in Burch's work and his method of wave form compensation led to the same result. Burch's earliest publication on the subject preceded Einthoven's by four years.

The dynamic characteristics of the capillary electrometer made it a direct mechanical analogue of the simplest kind of low pass electrical filter. Only the direct current component of an impressed signal came through unaltered. Time varying components were subject to lag and attenuation with output amplitude of specific sinusoidal content being progressively diminished for increasing frequencies.

Both Einthoven and Burch determined the dynamic parameters of the capillary electrometer by examining its response to a step input. They found this to be of the form

$$y = a(1 - e^{-bt})$$

where y is position of the meniscus shadow at time t after application of the step input, a is the ultimate value of y , e is the base of natural logarithm, and b is the all important decay constant of the system. Einthoven's meticulous measurements showed this relationship to hold true well within the limits of experimental error.⁴ In principle wave form restoration simply consists of adding to the recorded curve on a point by point basis $1/b$ parts of its first time derivative. Or, to exemplify the first derivative of the above response curve to unit step input is

$$y' = ab e^{-bt}$$

It follows directly from this that

$$y + y'/b = a$$

and thus the form of the applied step voltage is theoretically recovered. The validity of the method for all kinds of input signals is readily confirmed by the more rigorous forms of mathematical analysis which are in common use today.

Burch developed an ingenious graphic method of

structure which tautens abruptly in the wake of the rising ventricular pressure. Is it not reasonable to assume that such a sound is an opening snap of the aortic valve?

In summary therefore all hemodynamic and direct visual evidence continues to be consistent with the conclusion that the mitral snap is related to opening of the valve. We suspect that if Drs. Rodbard and Libanoff would re examine their own data they too might come to a similar conclusion.

Marion E. Tavel MD
Harvey Feinstbaum MD

Department of Medicine
Indiana University School of Medicine
Indianapolis Ind

REFERENCES

- 1 Marjolies A and Wolferth C C The opening snap (Claquement d'ouverture de la mitrale) in mitral stenosis its characteristics mechanism of production and diagnostic importance *AM HEART J* 7 443 1931 32
- 2 Ross R S and Criley J M Cineangiocardio-graphic studies of the origin of cardiovascular physical signs *Circulation* 30 255 1969
- 3 Friedman N J Echocardiographic studies of mitral valve motion Genesis of the opening snap in mitral stenosis *AM HEART J* 80:177 1970
- 4 Zak A Naser W A and Feigenbaum H A study of mitral valve action recorded by reflected ultrasound and its application in the diagnosis of mitral stenosis *Circulation* 37 789 1968
- 5 Epstein E J Criley J M Raftery E B Humphries J O and Ross R S Cine-radiographic studies of the early systolic click in aortic valve stenosis *Circulation* 31 842 1965
- 6 Whitaker A V Shaver J A Gray S and Leonard J J Sound pressure correlates of the aortic ejection sound *Circulation* 39 475 1969

Reply

To the Editor

Dr. Tavel and Feigenbaum state that virtually all authorities have accepted the view that the snap is *in some way* (my italics) related to opening of the mitral valve. However at least six different interpretations of the events after opening of the valve and prior to the snap have been offered by various authors as indicated in references 21 to 26 in our paper. For example Ross and Criley state that the snap occurs at the moment of first flow through the valve while Tavel and Feigenbaum hold that the mitral valve is open prior to the snap and that atrial pressure exceeds ventricular pressure for as much as 30 msec. Sullivan is pointed out by the rest of the majority of opening of the stenotic valve in mid-diastole. The latter mechanism cannot account for the snap heard in many conditions in which the aortic valve is in a subvalvular or aortic defect, ductus arteriosus, atrial myxoma or after exertion in some normal subjects (references 21 and 30 to 40 in our paper). The common

ment on the murmur of mitral regurgitation is not directly relevant to the question of the snap

They claim that direct studies of mitral movement by means of echocardiography and cineangiography do not support our idea that the previously opened mitral valve generates the snap as it closes momentarily during early systole. We seriously question the validity of their position as indicated below.

Echocardiography Tavel and Feigenbaum state that they have never observed echographic evidence for closure of either the anterior or posterior leaflet during early diastole. Limitations in the technique of echocardiography raise questions concerning their statement. The sound pulses are held to be a collimated or converging beam and the echo is assumed to be reflected from specific interface such as the anterior leaflet of the mitral valve. The actual reflections come from a broad arc of interfaces and the accumulated echoes for each distance are displayed as an apparent single echo.

At the time of the snap each of the components of the heart is involved in complex movements. Thus the runoff of arterial blood causes the aortic root to move superiorly, the septal muscle bundles begin to elongate, the mitral ring moves away from the apex and the mitral valve leaflets are pushed apart and atrioventricular flow begins as ventricular pressure falls below atrial pressure. The complex geometry of the resulting reflective surfaces and their changes with time diminish the likelihood that a particular portion of the surface of the anterior leaflet can be definitively identified as the sole or even the major source of the reflected signal. Zakly Nasser and Feigenbaum³ have recently recognized that a portion of the mitral valve movements may be generated by the base of the heart especially by the mitral valve ring. Strong echoes generated by surrounding extracardiac structures can also seriously complicate the tracing and its interpretation. The orchestra of echoes from many different moving surfaces forces the echocardiographer to direct the beam in various directions through a small intercostal portal until a pattern appears which he believes on the basis of experience to be the sole movements of the anterior leaflet of the mitral valve. Slight angulation or change in position of the transducer on the chest wall produces significant changes in the echo wave forms. The decision as to their sources has been stated. The echoes from the anterior leaflet of the mitral valve are determined by their location and timing with the opening snap. This standard is also reversed. The opening snap occurs after the sudden onset of (echocardiographic) mitral valve opening. Such internal calibrations do not offer certainty regarding the source of the recorded signals.

An even more serious question is exemplified in Tsvet and Feigenbaum's Fig. 1. Their trace may not properly represent the full train of echoes. The success is due from the 10000 cycles per sec. I usually vary greatly in amplitude suggesting that the interfaces may be chaotic rapidly. Displays of all of the echoes are usually highly irregular and difficult to analyze. These great irregularities are also evident in current publications.

Much clinical echocardiography avoids the form-

Letters to the Editors

The "closing snap" in mitral stenosis

To the Editor

After reading the article entitled "The mitral closing snap" by Drs Rodbard and Libinoff (*Am Heart J* 83:19, 1972) our reaction was one of utter consternation. Since at least the early 1930s when the elegant studies of Margolis and Wolferth clearly defined the characteristics of the mitral opening snap, virtually all authorities have accepted the view that this snap is in some way related to opening of the mitral valve. Moreover, it appears that the sound is generated at the time that the mitral valve first reaches its fully open position halting its forward movement abruptly.^{1,4}

Now Drs Rodbard and Libinoff attempt to debunk this principle by invoking certain pressure findings to support an opposing theory. Before we decide to consider these authors' conclusions very seriously, let us examine their data more closely.

Their observations provide evidence that the mitral valve is open prior to the snap. This does indeed agree with our data¹ and with those of others¹ who have shown that the valve has reached maximum opening coincident with the snap. This point occurs about 20 to 30 msec after the left ventricular pressure drops below the left atrial pressure in early diastole. Therefore, the earliest the snap might be expected to occur would be 20 or 30 msec earlier—not the entire 80 msec of isovolumic relaxation (interval between aortic closure and the usual opening snap) as suggested by Rodbard and Libinoff. They then suggest that since the snap ordinarily is so late, the mitral valve must have closed in order to cause the snap. Direct studies of the mitral movement with both cine angiocardioraphy² and echocardiography^{3,4} do not support such an assumption. We have looked at literally hundreds of echocardiograms of mitral valve motion in mitral stenosis and despite this technique's extremely high frequency response (up to 1,000 Hz) we have never observed closure of either the anterior or posterior leaflet in early diastole. All studies simply show that the leaflets have first reached their most open position (Fig. 1) at the time of the snap.

Rodbard and Libinoff go on to state that the snap is best heard superior to and somewhat to the right of the cardiac apex. This location supports the thesis that the sound may be louder in the atrium than in the ventricle. Unfortunately, one serious flaw in this line of reasoning is provided by the example of mitral regurgitation which produces a murmur located best in the left atrium. Such a murmur does not ordinarily have a location to the right and superior to the apex.

Rodbard and Libinoff state that 10 msec after the snap the atrial pressure rises and forms a notch and rise. This is analogous to the diastolic notch of the arterial pulse as closure of the aortic valve occurs. If this analogy were correct (and we suspect that it is) then one would expect the trough of the atrial

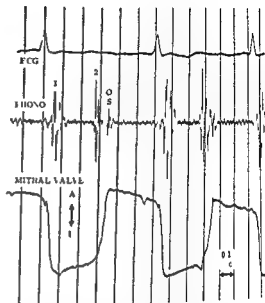


Fig. 1 Phonocardiogram (middle) with simultaneous echocardiogram of anterior leaflet of mitral valve (bottom) showing the opening snap (OS) occurring at the point that the mitral leaflet first reaches its fully open anterior position in early diastole. No closure occurs during diastole.

pressure notch to occur as the mitral leaflets suddenly cease to move away from the atrium (toward the ventricle) ending their opening motion. This would be truly analogous to the situation in which the aortic valve leaflets suddenly stop moving away from the aorta (toward the ventricle) reaching in this instance the end of their closing movement. The subsequent rise in pressure in the atrium and aorta following each notch would simply be a rebound phenomenon to the sudden cessation of motion.

Rodbard and Libinoff go even further to cast doubt on the thesis that opening motions of the valves are incapable of producing sharp sound. Their analogy here is to liken the mechanism to that of a door suddenly opening. This movement does not produce sound whereas closing does produce a sharp transient. Certainly this statement is true of normal doors but what of the stenotic door? Suppose we were to tie a cord from the doorjamb to the doorknob and permit the door to open just half way. The having been done a quick opening motion would result in the door's opening motion suddenly being arrested in mid flight. A sound would surely result from this checking motion. In this connection the maximum of the ejection click of valvular stenosis provides important insight. Is it too produced by closure of the semilunar valve? Certainly not! Accurate cineangiographic hemodynamic studies^{5,6} show that a sound is produced as the aortic leaflets reach their maximum (although retracted) open position forming a sail-like or domed

ature which tautens abruptly in the wake of the rising ventricular pressure. Is it not reasonable to assume that such a sound is an opening snap of the aortic valve?

In summary, therefore, all hemodynamic and direct visual evidence continues to be consistent with the conclusion that the mitral snap is related to opening of the valve. We suspect that if Drs. Poibard and Libanoff would re-examine their own data they too might come to a similar conclusion.

Morton E. Tavel MD
Harvey Feigenbaum MD
Department of Medicine
Indiana University School of Medicine
Indianapolis, Ind.

REFERENCES

- Margolis A and Wolferth C C. The opening snap (Claquement d'ouverture de la mitrale) in mitral stenosis: its characteristics, mechanism of production and diagnostic importance. *Am Heart J*, 44: 1931-32.
- Ross R S and Criley J M. Cineangiographic studies of the origin of cardiovascular physical signs. *Circulation* 30:755 1969.
- Friedman N J. Echocardiographic studies of mitral valve motion. Genesis of the opening snap in mitral stenosis. *Am Heart J* 80:177 1970.
- Zaky A, Nasser W K, and Feigenbaum H. A study of mitral valve action recorded by reflected ultrasound and its application in the diagnosis of mitral stenosis. *Circulation* 37:789 1968.
- Epstein F J, Criley J M, Raftery E B, Humphries J O, and Ross R S. Cineangiographic studies of the early systolic click in aortic valve stenosis. *Circulation* 31:842 1965.
- Whitaker A V, Shaver J A, Gray S, and Leinhardt J J. Sound pressure correlates of the aortic ejection sound. *Circulation* 39:475 1969.

Reply

To the Editor

Drs. Tavel and Feigenbaum state that "virtually all authorities have accepted the view that the snap is in some way (my italics) related to opening of the mitral valve." However, at least six different interpretations of the events after opening of the valve and prior to the snap have been offered by various authors as indicated in reference 21 to 6 in our paper.¹ For example, Ross and Criley² state that the snap occurs at the moment of first flow through the valve, while Tavel and Feigenbaum hold that the mitral valve is open prior to the snap,³ and that aortic pressure exceeds ventricular pressure for as much as 30 msec. before the snap generated by the onset of the motion of opening of the stenotic valve is noticed. The latter mechanism cannot account for the mitral snaps heard in many conditions in which there is no mitral stenosis, as in ventricular septal defect, ductus arteriosus, atrial myxoma, or after exertion in some normal subjects (references 21 and 30 to 40 in our paper).¹ The reason

ment on the murmur of mitral regurgitation is not directly relevant to the question of the snap.

They claim that direct studies of mitral movement by means of echocardiography and cineangiography do not support our thesis that the previously opened mitral valve generates the snap as it closes momentarily during early systole. We seriously question the validity of their positions indicated below.

Echocardiography. Tavel and Feigenbaum state that they have never observed echographic evidence for closure of either the anterior or posterior leaflet during early diastole. Limitations in the technique of echocardiography raise questions concerning their statement. The sonar pulses are held to be a collimated or converging beam, and the echo is assumed to be reflected from specific interfaces such as the anterior leaflet of the mitral valve. The actual reflections come from a broad arc of interfaces and the accumulated echoes for each distance are displayed as an apparent single echo.

At the time of the snap, each of the components of the heart is involved in complex movements. Thus the runoff of arterial blood causes the aortic root to move superiorly, the septal muscle bands begin to elongate, the mitral ring moves away from the apex, and the mitral valve leaflets are pushed apart, and ventricular flow begins as ventricular pressure falls below atrial pressure. The complex geometry of the resulting reflective surfaces and their changes with time diminish the likelihood that a particular portion of the surface of the anterior leaflet can be definitively identified as the sole or even the major source of the reflected signal. Zaky, Nasser, and Feigenbaum⁴ have recently recognized that a portion of the mitral valve movements may be generated by the base of the heart, especially by the mitral valve ring. Strong echoes generated by surrounding extracardiac structures can also seriously complicate the tracing and its interpretation. The orchestra of echoes from many different moving surfaces forces the echocardiographer to direct the beam in various directions through a small intercostal portal until a pattern appears which he believes on the basis of experience to be the sole movements of the anterior leaflet of the mitral valve. Slight angulation or change in position of the transducer on the chest wall produces significant changes in the echo wave forms. The decision as to their sources has been stated. The echoes from the anterior leaflet of the mitral valve are determined by their location and timing with the opening snap. This standard is also reversed. The opening snap occurs after the sudden onset of (echographic) mitral valve opening.⁵ Such internal vibrations do not offer certainty regarding the source of the recorded signals.

An even more serious question is exemplified in Tavel and Feigenbaum's Fig. 1. Their trace may not properly represent the full train of echoes. The occurrence of echoes from the 1000 impulses per second normally vary greatly in amplitude, suggesting that the interfaces may be changing rapidly. Displays of all of the echoes are usually highly irregular and difficult to analyze. These great irregularities are also evident in current publications.⁶

Much clinical echocardiography avoids the fore-

going difficulties by dropping the deviant signals. In oscilloscopic display, selective filtration⁸ smoothes the returning signal. This is also accomplished as a result of the persistence characteristics of the oscilloscope phosphor or the sensitivity of the photographic film. The echocardiograph thereby converts a succession of relatively irregular amplitudes of the stream of echoes into an esthetically pleasing, smooth tracing. This signal averaging suppresses information on brief episodes such as would occur on the sudden closing and reopening of valve leaflets. Looking at even thousands of such echocardiograms cannot reveal evidence of sudden movements of the valve leaflets during a transitory closure, since the recording system eliminates this evidence.

Sound recordings, pressure recordings and angiocardiography. Recent reports of simultaneously recorded sounds, pressures and cineangiograms are cited by Tavel and Feigenbloom as evidence against the concept of the closing snap. Ross and Criley's paper² on the origin of cardiovascular physical signs deals only briefly with the snap. The drawings based on cineangiograms are not suitable for analysis of the question. More pertinent are the data presented by Thompson and associates⁷ whose pressure and sound correlates of the mitral valve are similar to ours except that their apparatus divides the pressure signal arbitrarily at 40 Hz. The lower frequencies form a relatively smooth pressure wave while the higher frequencies are separated as the sound waves. The recorded simultaneity of the snap with the notch on the atrial γ descent and with the sudden acceleration of the rate of fall of ventricular pressure (Thompson's Fig. 12)⁷ is strong hydrodynamic evidence that the snap is produced at the instant when blood streaming through the mitral orifice is suddenly stopped by closing of the valve. These simultaneous events can in no way represent opening of the valve at the instant of the snap as Thompson and co-workers⁷ and Tavel and Feigenbloom suggest. Only the sudden closing of the valve leaflets will generate these physical phenomena.

Cineangiograms in Thompson's publication⁷ do not provide satisfying evidence that no contrast material enters the left ventricle prior to the snap. The silent hiatus of 15 msec between successive frames even at 60 angiographic frames per second impinges on the time domain in which information is sought. The picture is further complicated by the cineangiographic injections at very high pressures of materials of high density and viscosity procedures that commonly produce myocardial disturbances for several beats. Ambiguities introduced in the publication of frames obtained by these methods may have contributed to difficulties in identifying the discrete published frame in which retroventricular flow is said to have been initiated (Thompson's Figs. 9 and 11 and personal communication).

Tavel and Feigenbloom ask whether we believe that aortic ejection clicks and murmurs are also due to momentary valve closure. This has been our position for many years. Our hydrodynamic studies of the past two decades support the concept that the same physical principle that accounts for the mitral closing snap also generates aortic clicks and ejection murmurs.⁹

The foregoing analysis and the reasons expressed in detail in our manuscript reaffirm our conclusion that powerful hydrodynamic forces push the leaflets together and momentarily stop the previously moving stream thereby generating the mitral closing snap.

Simon Rodbard MD
Director, Cardiology Department
City of Hope National Medical Center
1500 E. Duarte Rd.
Duarte, Calif. 91010

REFERENCES

1. Rodbard S and Libinoff A J. The mitral closing snap. *Am Heart J* 83:19, 1972.
2. Ross R S and Criley J M. Cineangiographic studies of the origin of cardiovascular physical signs. *Circulation* 30:155, 1969.
3. Zaky A, Nasser W K and Feigenbaum H. A study of mitral valve action recorded by reflected ultrasound and its application in the diagnosis of mitral stenosis. *Circulation* 33:189, 1968.
4. Segal B L. Symposium on echocardiography. Introduction. *Am J Cardiol* 19:1, 1967.
5. Kingsley H, Flint G B Jr, Raber G T and Segal B L. Another look at echocardiography. *Am J Cardiol* 19:108, 1967.
6. Shih P M, Gramiak R, Adelman A G and Wigle E D. Echocardiographic assessment of the effects of surgery and propranolol on the dynamics of outflow obstruction in hypertrophic subaortic stenosis. *Circulation* 43:516, 1971.
7. Thompson M, Shaver J A, Heidenreich F P, Leon D F and Leonard J J. Sound pressure and motion correlates in mitral stenosis. *Am J Med* 49:436, 1970.
8. Rodbard S and Saiki H. Flow through collapsible tubes. *Am Heart J* 46:715, 1953.
9. Rodbard S. The production and physical qualities of sound in the cardiovascular system. In Segal B, editor. *The theory and practice of auscultation*. Philadelphia, 1963. F A Davis Company, pp 26-35.

Anticoagulants in pregnancy

To the Editor

The interesting editorial of Hirsh, Cade and Gillus (*Am Heart J* 83:301, 1972) on the subject of the role of anticoagulants in pregnancy has prompted me to review some of my early experiments on pregnant dogs which had been given Dicumarol during their last four days of gestation.¹ In one instance a litter of seven pups had a prothrombin time of about 200 seconds and the mother had a time of 21 seconds. The three pups that were given a water soluble vitamin K (Synkayvite) on their first day survived and their prothrombin time became normal in a week. The four untreated pups died of spontaneous internal hemorrhage. After 25 years it is now possible to offer an explanation for the observation.

Three basic concepts have to be considered: (1) Vitamin K is a growth vitamin needed also in the maintenance and repair of tissues. (2) Dicumarol

is an antagonist of vitamin K and depresses its metabolic function and (3) in both vitamin K deficiency and after Dicumarol the synthesis of prothrombin factors VII, IX, and X is depressed. Factor VII is diminished most and its diminution causes a faulty tissue maintenance which is the major cause of the spontaneous bleeding. The vitamin K requirement of the pup is many times greater than that of the adult dog. When therefore the vitamin K dependent synthetic enzyme is depressed the production of factor VII is no longer adequate to meet the requirement of tissue maintenance and hence the severe and spontaneous hemorrhage.

The only method which measures factor VII deficiency is the one stage prothrombin time and thus this is the only means to diagnose the hemostatic defect caused by anticoagulants. Factor VII is not required in the intrinsic blood coagulation system and therefore all other clotting tests are normal even in a severe deficiency of this factor. Factor VII is a co-factor of tissue thromboplastin and not a true coagulation factor hence former designations such as stable factor and proconvertin are no longer justified.

Armand J. Quick, M.D.
Hemostasis Research Laboratory
Medical College of Wisconsin
Milwaukee, Wisc 53233

REFERENCES

1. Quick, A. J. Experimentally induced changes in the prothrombin level of the blood III Prothrombin concentration of newborn pups of a mother given Dicumarol before parturition. *J Biol Chem* 164:371, 1946.
2. Quick, A. J., Collentine, G. M., and Hussey, C. V. Vitamin K requirements of the growing pup. *J Nutr* 7:8, 1967.

Digitalis intoxication

To the Editor

I have read with interest the editorial "Non cardiac symptoms of digitalis intoxication" by

V. H. Lely and C. H. J. van Lenter, which appeared in the February 1972 issue of the *JOURNAL* (83:14, 1972).

In the VII Central American Congress of Medicine held here in Tegucigalpa in December 1967 we reported the high incidence of visual disturbances in digitalis intoxication. In a prospective study we observed 34 cases in which there were 73 cases showing color vision a 67 per cent incidence. This is not as high as the 95 per cent rate reported by Drs. Lely and van Lenter but certainly it is indicative of the high incidence of this cardiac manifestation in digitalis intoxication.

Other studies have shown a lower incidence of visual disturbances.^{1,2} It is my impression that chromatopsia is a very early manifestation of digitalis toxicity. It is our experience that when properly investigated color vision is found in one of the initial symptoms of digitalis intoxication. Yellow vision (xanthopsia) was present as the most common visual abnormality in our study.

The presence of visual disturbances should be investigated in patients taking digitalis as this is an early symptom of digitalis toxicity. This is particularly true in older patients who are apparently more prone to suffer this disturbance.

Alfredo Leon Gomez, M.D.
Professor of Medicine
Universidad de Honduras
La Piedad
Tegucigalpa, Honduras

REFERENCES

1. Lely, V. H. and van Lenter, C. H. J. Non cardiac symptom of digitalis intoxication. *AM HEART J* 83:149, 1972.
2. Gomez, A. Leon. La vision coloreada en intoxicacion digitalica. Memoria VII Congreso Medico Centroamericano 1967 Tegucigalpa Honduras C. A.
3. Dubnow, M. H. and Burchell, H. B. A comparison of digitalis intoxication in two separate periods. *Ann Intern Med* 62:950, 1967.
4. Lyon, A. F. and DeGraff, A. C. The neurotoxic effects of digitalis. *AM HEART J* 65:839, 1963.

gony difficulties by dropping the deviant signals. In oscilloscopic display selective filtration³ smooths the returning signal. This is also accomplished as a result of the persistence characteristics of the oscilloscope phosphor or the sensitivity of the photographic film. The echocardiograph thereby converts a succession of relatively irregular amplitudes of the stream of echoes into an esthetically pleasing smooth tracing. This signal averaging suppresses information on brief episodes such as would occur on the sudden closing and reopening of valve leaflets. Looking at even thousands of such echocardiograms cannot reveal evidence of sudden movements of the valve leaflets during a transitory closure since the recording system eliminates this evidence.

Sound recordings pressure recordings and angiography. Recent reports of simultaneously recorded sounds pressures and cinematograms are cited by Tiveli and Eigenbaum as evidence against the concept of the closing snap. Ross and Criley's paper² on the origin of cardiovascular physical signs deals only briefly with the snap. The drawings based on cinematograms are not suitable for analysis of the question. More pertinent are the data presented by Thompson and associates⁷ whose pressure and sound correlates of the mitral valve are similar to ours except that their apparatus divides the pressure signal arbitrarily at 40 Hz. The lower frequencies form a relatively smooth pressure wave while the higher frequencies are separated as the "sound waves." The recorded simultaneity of the snap with the notch on the atrial pressure and with the sudden acceleration of the rate of fall of ventricular pressure (Thompson's Fig. 12)⁷ is strong hydrodynamic evidence that the snap is produced at the instant when blood streaming through the mitral orifice is suddenly stopped by closing of the valve. These simultaneous events can in no way represent opening of the valve at the instant of the snap as Thompson and co-workers⁷ and Tiveli and Eigenbaum suggest. Only the sudden closing of the valve leaflets will generate these physical phenomena.

Cineangiograms in Thompson's publication⁷ do not provide satisfying evidence that no contrast material enters the left ventricle prior to the snap. The silent hiatus of 15 msec between successive frames even at 60 angiographic frames per second impinges on the time domain in which information is sought. The picture is further complicated by the cineangiographic injections at very high pressures of materials of high density and viscosity procedures that commonly produce myocardial disturbances for several beats. Ambiguities introduced in the publication of frames obtained by these methods may have contributed to difficulties in identifying the discrete published frame in which atrioventricular flow is said to have been initiated (Thompson's Figs. 9 and 11 and personal communication).

Tiveli and Eigenbaum ask whether we believe that aortic ejection clicks and murmurs are also due to momentary valve closure. This has been our position for many years. Our hydrodynamic studies of the past two decades support the concept that the same physical principle that accounts for the mitral closing snap also generates aortic clicks and ejection murmurs.^{2,8}

The foregoing analysis and the reasons expressed in detail in our manuscript reaffirm our conclusion that powerful hydrodynamic forces push the leaflets together and momentarily stop the previously moving stream thereby generating the mitral closing snap.

Simon Rodbard MD
Director, Cardiology Department
City of Hope National Medical Center
1500 E. Duarte Rd.
Duarte, Calif. 91010

REFERENCES

1. Rodbard S and Libinoff A J. The mitral closing snap. *Am Heart J* 83:19 1971.
2. Ross R S and Criley J M. Cineangiographic studies of the origin of cardiovascular physical signs. *Circulation* 30:755 1969.
3. Zaky A, Nasser W K and Eigenbaum H. A study of mitral valve action recorded by reflected ultrasound and its application in the diagnosis of mitral stenosis. *Circulation* 37:189 1968.
4. Segal B I. Symposium on echocardiography. Introduction. *Am J Cardiol* 19:1 1967.
5. Kinsley B, Flint G B Jr, Raber G T and Segal B I. Another look at echocardiography. *Am J Cardiol* 19:108 1967.
6. Shah P M, Grumak R, Adelman A G and Wigle L D. Echocardiographic assessment of the effects of surgery and propranolol on the dynamics of outflow obstruction in hypertrophic subaortic stenosis. *Circulation* 45:516 1972.
7. Thompson W E, Shaver J A, Heidenreich F P, Leon D F and Leonard J J. Sound pressure and motion correlates in mitral stenosis. *Am J Med* 19:436 1970.
8. Rodbard S and Suki H. Flow through collapsible tubes. *Am Heart J* 46:715 1953.
9. Rodbard S. The production and physical qualities of sound in the cardiovascular system. In Segal B, editor. *The theory and practice of auscultation*. Philadelphia 1964. L. A. Davis Company, pp 26-35.

Anticoagulants in pregnancy

To the Editor

The interesting editorial of Hursh Cade and Gillis (*Am Heart J* 83:301 1972) on the subject of the role of anticoagulants in pregnancy has prompted me to review some of my early experiments on pregnant dogs which had been given Dicumarol during their last four days of gestation.¹ In one instance a litter of seven pups had a prothrombin time of about 200 seconds and the mother had a time of 21 seconds. The three pups that were given a water soluble vitamin K (Synkayvite) on their first day survived and their prothrombin time became normal in a week. The four untreated pups died of spontaneous internal hemorrhage. After 25 years it is now possible to offer an explanation for the observations.

Three basic concepts have to be considered: (1) Vitamin K is a growth vitamin needed also in the maintenance and repair of tissues. (2) Dicumarol

Books received

CLINICAL PHARMACOLOGY—BASIC PRINCIPLES IN THERAPEUTICS Edited by Kenneth L. Melmon MD and Howard F. Morrell MD New York 1972 The Macmillan Company 718 pages Price \$16.00 (Also available in paperback at \$11.95)

CORONARY HEART DISEASE—A NEW ZEALAND REPORT A report to the National Heart Foundation of New Zealand 1971 from a committee convened by the Scientific Committee of the Foundation The National Heart Foundation of New Zealand 1971 79 pages

MANAGEMENT OF ARTERIAL OCCLUSIVE DISEASE Edited by W. Andrew Dale MD Based on a conference held at Nashville Tennessee sponsored by the Vanderbilt University School of Medicine St. Thomas Hospital Baptist Hospital and Johnson & Johnson Chicago 1971 Year Book Medical Publishers Inc 506 pages Price \$25.00

MEDICAL RECORDS MEDICAL EDUCATION AND PATIENT CARE By Lawrence L. Weed MD Chicago 1971 The Press of Case Western Reserve University distributed by Year Book Medical Publishers Inc 297 pages

STÖRUNGEN DES ARTERIELLEN HERZENDES MORPHOLOGIS UND MORPHOGENESE (Malformations of the Arterial End of the Heart. Morphology and Morphogenesis) By Hans Bock München Berlin and Wien, 1971 Urban & Schwarzenberg 135 pages

MISSBILDUNGEN DES HERZEN UND DER GROSSEN GEFÄSSE By Karl Bock, Heinz Tenckmann, Martin Herbst, and Ferdinand Spreer Berlin 1971 VEB Verlag Volk und Gesundheit 586 pages

BLOOD MICROHEMOLOGY—VISCOSITY FACTORS IN BLOOD FLOW ISCHEMIA AND THROMBOSIS By

Leopold Dintenfass PhD MSc FRACI MIE Aust Toronto 1971 Butterworth & Co Ltd 445 pages Price \$19.25

CARDIAC SURGERY 2 Cardiovascular Clinic Vol 3 No 3 Guest Editor Dwight F. Harken MD Philadelphia 1971 F. A. Davis Company 184 pages Price \$12.00

CLINICAL PHONOCARDIOGRAPHY AND EXTERNAL PULSE RECORDING Ed 2 By Morton E. Tavel MD Chicago 1972 Year Book Medical Publishers Inc 329 pages

FROM CARDIAC CATHETERIZATION DATA TO HEMODYNAMIC PARAMETERS By Sing San Yang MD L. G. Bentivoglio MD MS Viadri Maranhao MD and Harry Goldberg MD Philadelphia 1972 F. A. Davis Company 307 pages Price \$12.00

POSTOPERATIVE CARDIAC INTENSIVE CARE Ed 2 By M. V. Braumbridge MA MB BChir FRCS Oxford London and Edinburgh 1972 Blackwell Scientific Publications (distributed in the USA by F. A. Davis Company Philadelphia) 176 pages Price \$9.00

SYMPOSIUM ON CARDIOMYOPATHY (Pamphlet) Reprinted from *Circulation* November 1971 Vol XLIV No 5 New York 1972 American Heart Association Inc 33 pages Price \$1.00

THERAPY IN ACUTE CORONARY CARE By Barry B. White MD Chicago 1971 Year Book Medical Publishers Inc 156 pages Price \$10.95

SYSTEMATIC INJURIES OF THE HEART AND GREAT VESSELS By Panagiotis N. Symbas MD Springfield 1972 Charles C. Thomas Publisher 188 pages Price \$14.00

Announcements

Czechoslovakian Surgical Congress

The J. E. Purkyně Czechoslovakian Medical Society will sponsor an international Czechoslovakian Surgical Congress to be held in Bratislava Czechoslovakia on July 13 and 14, 1973. Topics to be treated will be surgery of acute and chronic pancreatitis, polytraumatism and its life-endangering consequences, angioplasty and various other related subjects.

Persons desiring further information should contact The Secretariat, Congress Office, Slovak Medi-

cal Society Bratislava Mladá Mladá 18 Czechoslovakia.

Jane Nugent Cochems Competition

The University of Colorado School of Medicine announces the Eleventh Annual Cochems Competition funds for which were provided in the will of the late Mrs. Jane Nugent Cochems. A prize of \$2,500 will be awarded to the author of the best paper in the field of Thrombophlebitis and Basic Vascular

Book reviews

GOLDEN'S DIAGNOSTIC RADIOLOGY Section 18. SELECTIVE ANGIOGRAPHY. Laurence I. Robbin. Editor. William N. Harnsbee. Section Editor. The Williams & Wilkins Company. Baltimore. 1972. 332 pp. Price \$25.00.

The 18th section of the Golden Series on Diagnostic Radiology is devoted to the use of angiology to outline the circulation to specific organs and areas of the body. This field of medicine is developing rapidly and new techniques and applications are appearing rapidly. This issue of the series is concerned with seven major aspects: (1) fundamentals of selective angiography, (2) selective angiography of the abdominal viscera, (3) coronary angiography, (4) head and neck, (5) peripheral vascular, (6) adrenal and (7) renal. The respective applications are carefully and thoroughly discussed. The illustrations are extremely good and well selected and the annotated legends and text are concise and clear. This is a good book that should interest cardiologists and cardiovascular surgeons as well as radiologists.

HANDBOOK OF EXPERIMENTAL PHARMACOLOGY Band XXXI. ANGIOTENSIN DRUGS. Pathophysiological, Hemodynamic, Methodological, Pharmacological, Biochemical and Clinical Basis for Their Use in Human Therapeutics. By R. Christer. New York. 1971. Springer Verlag. 442 pp. Price \$48.60.

This volume of the Handbook of Experimental Pharmacology dealing with antihypertensive drugs should interest all cardiologists and practicing physicians. The book presents a good summary of coronary atherosclerosis, the pathophysiology of angina pectoris, the hemodynamic basis of coronary pharmacology, testing, and action of coronary vasodilators as well as the use and action of supporting drugs such as morphine, sedatives, vitamins, antiarrhythmic agents, alcohol, and others. With over 2,300 references cited and well prepared author and subject indices, this is a valuable and useful reference work as well as a book that should be studied. We highly recommend this book to everyone interested in the subject.

CLINICAL CARDIOLOGY Third Edition. By V. SCHIRRE. M.Sc., Ph.D., M.D. (Cape Town), F.R.C.P.E., F.R.C.P., F.A.C.C. Harper & Row Publishers. New York. 1971. 658 pp. Price \$15.00.

The publication of this third edition of Clinical Cardiology indicates the excellent reception of the previous editions. Small by comparison to the other editions, this book represents the opinions and practices of an outstanding cardiologist who has been a leader in South African cardiology for many years. The presentations are clear and simple. The book is clinically oriented throughout and is written for the practicing doctor. It incorporates the experiences of

Dr. Schirre and his approach to patients with heart disease. All physicians will find this an important contribution to practical clinical cardiology to be a valuable book and it will be especially useful for internists and general practitioners.

✓ **CARDIAC SURGERY** 2. CARDIOVASCULAR CLINICS. Series Volume 3. Number 3. Albert N. Brecht, M.D., Editor in Chief. Dwight E. Harken, M.D., Guest Editor. F. A. Davis Company. Philadelphia. 1971. 184 pp. Price \$12.00.

This is the second volume in the Cardiovascular Clinics series devoted to cardiac surgery. The reader will find this book to contain good summaries of the present status of the surgical approach to the management of cardiovascular disease. A number of problems are discussed. Among these is a report by Effler on cardiac revascularization, an active surgical approach to coronary heart disease. Resectional therapy in infarction, assisted circulation, pacemakers, tumors of the heart, cardiac trauma, cardiac transplantation, and the mechanical heart are among the many presentations briefly treated in this volume. The Cardiovascular Clinics series continues to be interesting, valuable, practical, and timely. This is another good publication in the group.

✓ **A HANDBOOK OF ELECTROCARDIOGRAPHY** Sixth Edition. By George E. Burch, M.D., and Travis Winsor, M.D. Philadelphia. 1972. Lea & Febiger. Publisher. 292 pp. Price \$7.75.

Now in its sixth edition, this monograph has become a classic in cardiology. Its purpose is to provide the reader with knowledge of electrocardiography, beginning with basic principles of electrophysiology, leading to intelligent analysis of electrocardiograms and ultimately to clinical applications of the science. The presentation is systematic, well organized, lucid, and in spite of being comprehensive, is beautifully concise. It is a perfect text for the beginner in electrocardiography. Even for the individual with experience in the field, much can be gained from the book through solidification of knowledge based on well confirmed, sound electrophysiologic principles. By design, the authors have excluded controversial issues and new and untested concepts. Through this and other means, they have provided the opportunity for one of the most favorable reader time to information gained ratios available in print on this subject.

This reviewer could find no significant criticism to direct toward the book. It has truly met its purpose as a primer and can be recommended without reservation in that capacity. Binding, printing, and illustrations are excellent and the price is attractive.

Editorial

The cardiac patient and hemodynamics

Abraham Noordergraaf Ph D

Rotterdam and Delft The Netherlands

Clinicians and physiologists interested in the cardiovascular field designed their own instruments and formulated their own theories until perhaps 1940. Thus Einthoven¹ designed his own string galvanometer for the recording of the electrocardiogram and Forssmann² and later Courmand and Ranges³ demonstrated the safety of placing the catheter tip within or close to the heart for the measurement of blood pressure.

On the theoretical side the physician Thomas Young in the Croonian Lecture⁴ given in 1809 argued against what he supposed to be an almost universally held belief that contraction of arterial wall muscle was an important factor in pulse wave propagation. In 1850 Weber⁵ a physiologist took a strong position against those who believed that the pulse appeared in all parts of the body simultaneously.

Leaders of such stature had to take what professional help they could get. Einthoven had for a number of years a physicist by the name of Bergmans in his employment while Weber consulted with one of his brothers who was trained in mathematics.⁶ Put it was not until new technologies such as electronics became available that the design and construction of new smaller more delicate and more sophisticated instruments developed into a profession whose aim was to accurately measure

biomedical quantities for the first time or at least more reliably than had been possible before. Those accepting this challenge have been trained as physicists or more frequently as engineers. The members of this group now look on themselves as medical physicists or as biomedical engineers and their chief concern is to provide better instruments for clinicians for physiologists and for others who work in various areas of the life sciences. The success of many of these instruments such as the pacemaker and the defibrillator testifies to the pragmatic abilities of this group. In this same category are those individuals who adapted the computer to problems in the clinical sciences such as patient monitoring.

Another quite distinct field has attracted investigators who failing to find fulfillment in instrumentation decided to look into the biological phenomena themselves. Its subject matter can be classified under the heading of fundamental biomedical engineering or more properly under biophysics. One of the areas in which these investigators are concerned has yielded results that are of immediate interest to cardiovascular clinicians and physiologists. The remainder of this article is devoted to these results and to their implications.

Seventy years ago Frank⁷ a physiologist with a practical mind was seeking a method

From the Thoracic and Medical School of Rotterdam, Rotterdam and the Physics Laboratory Institute of Technology Delft The Netherlands.
Received for publication June 28, 1971.
Key words: catheterization, D. Abraham Noordergraaf, Department of Biomedical Engineering, The University of Pennsylvania, Philadelphia, Pa. 19104.

Problems Basic vascular problems under consideration in this instance should be concerned with the underlying mechanisms or processes of vascular disease particularly those associated with thrombosis but not necessarily restricted to it

The competition is open to all persons holding the doctorate degree and entries must be received in triplicate including all charts illustration and photographs on or before November 15 1972 For income tax reasons eligibility is limited to those physicians who are subject to U.S. income tax regulations

No entry blank or application form is required There are no restrictive rules regarding length or format of the manuscript joint authorship or in-

clusion of such materials as pictures charts figures etc It is not required that the paper include results of original experimental work nor that it be based on personal clinical experience All manuscripts must be typed with double spacing and each copy together with accompanying illustration etc must be submitted in a folder or cover On request the original copy of the manuscript will be returned if accompanied by a stamped addressed envelope Papers will be judged on originality content clarity and critical value

Inquiries regarding the competition and all manuscripts should be submitted to the Dean School of Medicine University of Colorado Medical Center 4200 E Ninth Ave Denver Colo 80210

that Frank occupied himself with wave transmission studies during the latter part of his impressive career.

Recent studies have shown that the windkessel and transmission theories can be reconciled. Starting out from a set of equations that govern the motion of a viscous fluid in distensible vessels and taking into account the architecture of the arterial tree it is now possible to understand why the pulse wave velocity has the observed magnitude as well as to know the reason behind the changing shape of pressure and flow pulses as they travel away from the heart. In terms of frequency it has become clear why low frequency components travel much faster than high frequency components. This last finding is directly related to the old idea underlying the windkessel theory—that all pressure oscillations in the arterial tree occur almost simultaneously. For low frequencies this may indeed be stated with a fair degree of accuracy; for higher frequency components it is not true at all. For high frequency components of the pulse the arterial tree in its relation to the ventricle approximates the behavior of a distensible tube free of reflection. Therefore both the old windkessel theory and the single elastic tube theory (with or without reflection at the distal end of the tube) emerge as only special instances of a more general wave transmission theory in which the architecture of the arterial tree is a key element.⁶

This development has significance in several ways. It not only increases our understanding of the events in the systemic arterial tree but it also points the way to the solution of important practical problems. A few of these deserve mention here.

Recent developments

In the past a great deal of effort has been devoted to the experimental determination of the pulse wave velocity in patients for the purpose of evaluating the compliance of the larger arteries. The results usually suffered from a high variability. On the basis of the recent research summarized above it would seem that meaningful data on the actual phase veloc-

ity can be secured only from the fast components of the pressure pulse; the speed of the slow components is very sensitive to wave reflection and therefore to the value of the peripheral resistance. A pulse wave velocity derived from such components of larger amplitude leads necessarily to an apparent wave velocity which is consequently not a measure of the wall properties alone.

The research that led to the present level of our understanding of the events in the systemic arterial tree was much aided by the utilization of very elaborate simulation schemes. These are in fact too large to permit convenient programming on contemporary computers.⁶ Fortunately it appears that in general there is no need for a detailed programming of an entire model. If the problem under consideration does not require a detailed knowledge of the local pulse wave velocity in each of the larger arteries the program can be reduced substantially and in a logical fashion without significant loss of accuracy.¹⁰ The extent of the reduction depends on the questions posed. In most cases handling of the model is within reach of standard analog and digital computers. As a result a wider community of investigators will be able to utilize better models of the arterial trees in their own physiological or clinical work in arterial problems than were available in the past.

In the event that one wishes to formulate only the properties of the arterial tree in its relation to the left ventricle the solution is even simpler. One can deduce logically that the input impedance of the systemic arterial tree can with a good approximation be represented by a series combination of the characteristic impedance of the proximal part of the aorta and the old windkessel approach. Therefore this model (called the *u-estkessel*)¹⁰ contains only three elements each of which has a clear cut physiological meaning. By virtue of its simplicity it can be programmed easily on any type of computer or it can be cast in hydraulic form. This has direct implications for the solution of intricate problems. For as long as physiologists and clinicians have interested themselves in the performance of the heart as a pump the ventricle s-

which would enable him to assess the quality of the heart as a pump. He selected left ventricular stroke volume as the best parameter to characterize cardiac performance and developed the "windkessel theory" (originally proposed by Stephen Hales) to provide a basis for his formulations. His theory conceives of the aorta and its many branches as an elastic reservoir with a large outflow resistance. The heart pumps into this reservoir in an intermittent fashion, causing the pressure to oscillate. Frank proposed a way to derive the stroke volume from this pressure, which was required by a noninvasive technique. The approach had wide appeal and during the first several decades of the twentieth century Frank's school produced an abundance of variations on his original windkessel theory, each variation leading to a different formula for estimating stroke volume. Many publications almost exclusively in German resulted.

When Frank's school was at the peak of its fame, studies of wave transmission through arteries initiated much earlier by Euler were resumed by Witzig,² who proved himself a master in the field. At first ignored by most physiologists and clinicians, these studies were pursued and came to prominence in the period after World War II when interest in the windkessel theory waned. Wave transmission theory deals with pulse wave velocity, wave attenuation, and wave reflection in an arterial tree; hence it is mathematically oriented.

Although Ernst H. Weber had no difficulty in recognizing both windkessel and wave transmission effects in the systemic arterial tree, the attitudes of the advocates of the two theories became rather hostile. The proponents of the windkessel theory argued that the transmission theory, though perhaps more sophisticated, was useless to the clinician, and the transmission people countered by declaring that the confusing variety of stroke volume formulas gave poor results because they were based on an overly simplified concept of the arterial tree. Unquestionably, there was much truth in what each party had to say about the other.

The need for repeated estimates of the

state of cardiac function in intensive care units has brought this unsatisfactory state of affairs into sharp focus, especially since the number of these units is increasing rapidly. It is obvious that in many severe clinical conditions the common clinical tests (pulse rate, systolic and diastolic blood pressures, ECG, and VCG) do not provide the information necessary for a rational selection of therapeutic measures and for the judgment of their effects. To meet this need it has been considered mandatory to view the behavior of the circulation as a system rather than just look at stimulus conduction, continuous or semicontinuous monitoring of quantities providing information about fluid dynamics is what is required.

Owing to the progress made by those working in the instrumentation field, blood pressure can now be continuously recorded with a high degree of accuracy at virtually any site in the cardiovascular system. But knowledge of blood pressure itself does not reveal either cardiac output or stroke volume; if flow impedance is unknown. It is at this point that major difficulties are encountered, since the instrumentals to have not yet produced a flow meter suitable for the monitoring of flow in the seriously ill patient.

The clinician needs a way of obtaining flow data on a continuous or semicontinuous basis. In their efforts to solve this problem, it is interesting to note that investigators are rediscovering the approaches that rest on the old windkessel theory. However, the incisive criticisms directed against this theory still apply.

It was once suspected that the wave transmission theory had little if anything to offer which would permit or improve estimates of stroke volume in the clinic, but this cannot be sustained today. Intensive studies of the wave transmission properties of the human systemic arterial tree have brought out what Weber sensed but could not formulate quantitatively: that some aspects of the observed pressure changes are related to the windkessel and others to pulse propagation. If it is true that both aspects are real, it should be possible to interpret them on the basis of a single more general theory. It is of interest to note

9. Åpén, A. Hemodynamical studies. Scand Arch Physiol 111 (Suppl 16): 1940
10. Westerhof N and Noordergraaf A. Reduced models of the systemic arteries. In: Proceedings of the eighth international conference on medical and biological engineering. Chicago 1969
11. Starlin E H. The Linacre lecture on the law of the heart. Cambridge University 1915. London 1918. Longmans Green & Co. Ltd
12. Starr I. Studies made by simulating systole at necropsy. I. A test of the aortic compression chamber hypothesis and of two stroke volume methods based upon it. J Appl Physiol 11:169 1957

"load," which obviously affects the time course of the myocardial contraction process,¹¹ has had a puzzling identity. It has been variously taken as the value of the peripheral resistance, the arterial pressure operating as counterpressure (in the stand-ard heart lung preparation, one is varied to control the other¹²), the inertia of the blood in the central aorta, the compliance of the aorta, and other quantities as well. The reason for this is obvious enough, in the past it has been difficult, if not impossible to describe quantitatively what the ventricle "senses," particularly when one wants to study the transient effects during a single systole. Clearly, all of the above quantities play a role. The westkessel model may well offer a way out of this entangled issue by providing a first step in unravelling the significance of the several factors involved. This model not only presents the ventricle with the appropriate input impedance but also with the proper counterpressure.

This particular three element representation of the input impedance, valid for the frequency range being studied (including zero frequency where the input impedance is virtually equal to the peripheral resistance) is of immediate interest for a different reason. It would permit semi continuous stroke volume determination in the intensive care unit. For this application three elements are required: recorded root aortic pressure, the westkessel model, and any small computer capable of solving for changes in stroke volume in a semi continuous fashion. The values of the elements that make up the model proceed from adjustment for zero flow during diastole, while a single measurement of cardiac output by another technique would provide for absolute values of stroke volume and peripheral resistance. Without the latter, changes in stroke volume should be readily identifiable. It may be interesting to note here that many of the old windkessel based formulas for stroke volume contain the first element of the westkessel model, the aorta's characteristic impedance. This has in fact been argued to be the only valuable part of such formulas.¹²

This line of thought holds an additional promise. By virtue of the way it is consti-

tuted, the contour of the ejection curve itself is recorded, not just the curve's time integral, the stroke volume. Evidence that the shape of this curve reflects the contractile properties of the ventricle has been repeatedly presented in the literature.

Summary

Frank's windkessel model, as well as the single elastic tube model, have proved to be special cases of a wave transmission theory which is based on equations governing the motion of a viscous fluid in an arborized system of distensible tubes. The applicability of the windkessel theory proves to be restricted to the lowest frequencies of interest, which is why windkessel based formulas for stroke volume determination have been unsatisfactory. A new approach with a solid foundation in hemodynamic theory is needed to fill the recognized need for evaluation of the left ventricle as a pump. Surely problem solving in a real world should rely on our deepened insight into the properties of the cardiovascular system and not on ideas that belong to days gone by, that have long been in need of revision. The more general theory advanced here offers such solutions, some of which are outlined in some detail.

REFERENCES

- 1 Einthoven W. Un nouveau galvanomètre. *Arch Neerl Sci Exp Nat* part 6 The Hague 1901 Nijhoff.
- 2 Forssmann W. Die Sondierung des rechten Herzens. *klin Wochenschr* 8:7083 1919.
- 3 Courmand A and Ranges H S. Catheterization of the right auricle in man. *Proc Soc Exp Biol* 46:162 1941.
- 4 Young T. The Croonian lecture on the functions of the heart and the arteries. *Phil Trans London* 1809.
- 5 Weber C H. Über die Anwendung der Wellenlehre auf die Lehre vom Kreislaufes des Blutes und ins besondere auf die Pulslehre. *Berl Math Physik Cl Konigl Sächs Ges Wiss Berlin* 1850.
- 6 Noordergraaf A. Hemodynamics in Schwan H P editor. *Biological engineering* New York 1969 McGraw Hill.
- 7 Frank O. Die Grundform des arteriellen Pulses. *Biol* 37:483 1899.
- 8 Witzig K. Über erzwungene Wellenbewegungen zäher Inkompressibler Flüssigkeiten in elastischen Röhren. *Bern* 1914 Ph D thesis University of Bern.

Table 1 Valvular tissues excised and reviewed 1962-1973

Tissue	No	Men	Women
Aortic valve only	137	112 (82%)	25 (18%)
Mitral valve only	183	62 (34%)	121 (66%)
Tricuspid valve only	5	3	2
Aortic and mitral valves	13	6	7
Mitral and tricuspid valves	6	3	3
Total	344	186 (54%)	158 (46%)

fixed in cacodylate buffered 2.5 per cent glutaraldehyde (pH 7.2) for one to two hours. After rinsing in buffer the pieces were post fixed for one hour in 1 per cent cacodylate buffered OsO_4 , dehydrated rapidly in graded acetone and embedded in Vestopal W. One micron sections stained with toluidine blue were used for the selection of representative areas. Sections were then cut with glass knives on LKB Ultratome III. They were double stained with uranyl acetate and lead citrate and examined in a Hitachi 8S electron microscope at an electron optical magnification of from $\times 16,000$ to $\times 108,000$. The micrographs were enlarged photographically as needed.

The charts and office records of all patients in whom severe myxoid degenerative changes had been demonstrated were reviewed for the preoperative and cardiac catheterization diagnosis, evidence by history or physical examination of rheumatic fever, Marfan's disease or arachnodactyly, the operative and postoperative diagnosis and the results of the surgical treatment. The clinical and pathologic data were then correlated.

Results

The case material is summarized in Table 1. The 344 cases reviewed include 186 men and 158 women patients. The men patients ranged in age from 15 to 78 years and the women ranged from 16 to 74 years. The mean age for both sexes was 52 years. Men patients constituted over 80 per cent of those undergoing excision of the aortic cusps but they only made up one third of the patients undergoing excision of the mitral leaflets.

The microscopic study of the excised valves demonstrated the presence of cal-

cium in 192 cases. This does not indicate the actual incidence of calcification because in many instances calcified portions of the excised tissue were not used for microscopic examination. The actual incidence is found on review of gross descriptions is higher.

Two hundred forty three or 70 per cent of the tissues showed some degree of inflammation. In three instances there was a marked or diffuse infiltration by polymorphonuclear leukocytes but in the vast majority of cases there were only few focal collections of lymphocytes. This was often seen adjacent to or associated with areas of calcification. Aschoff bodies were found in seven cases. They were few in number, old and inactive. Most were characterized by zones of fibrosis and scarring with the presence of few Anitschkow myocytes and lymphocytes. Characteristic rheumatic vegetations were not seen. Vascularization of the valvular tissues was often prominent and in a number of cases there were distinct delicate papillary projections partially covered by endothelial cells.

Table II summarizes the myxoid changes observed. They were present in 73 per cent of all cases with equal frequency in aortic and mitral valve tissues. Most of the valves showed only minimal or slight changes. These were characterized by focal areas of vacuolization and the presence of occasional elongated or stellate cell forms. The myxoid changes were classified as severe only if they were extensive. This classification was by necessity arbitrary since it was principally based on the extent rather than on the qualitative change observed. In most of the cases classified as severe a band like area of myxoid degeneration extended through a central or subendocardial portion

Myxoid changes in cardiac valves pathologic, clinical, and ultrastructural studies

William H Kern MD*

Bernard I Lucker MD**

Los Angeles Calif

Myxoid or mucinous degenerative changes associated with insufficiency of the aortic or mitral valve have been recently described individually and in small series.¹⁻⁴ Some authors feel that the myxoid changes are nonspecific⁴ or the end result of many factors.⁵ Others propose a separate disease process possibly a forme fruste of Marfan syndrome.^{10,11} In some series the aortic valve was reported to be predominantly or exclusively involved,^{1,4,5} whereas in others the mitral valve was more frequently diseased.^{2,7,8,10} Because of the clinical significance of this lesion and the questions that have been raised concerning its nature, the frequency, degree, and significance of myxoid degenerative changes were evaluated in a large number of surgically excised cardiac valves and the pathologic and ultrastructural features were studied.

Materials and methods

Slides from all cases of surgically excised cardiac valves for the period from January 1, 1962, to June 30, 1971 were reviewed.

The review was conducted blindly without access to patient identification or clinical data. Of the 365 recorded cases a preliminary examination excluded 21 for lack of adequate tissue sections. The hematoxylin and eosin stained slides and special stains of the remaining 344 cases were examined. The presence or absence of fibrosis, calcification, inflammation, Aschoff bodies, and myxoid changes was recorded. The changes were graded from 1 to 3+; 1+ representing minimal change, 2+ moderate change, and 3+ severe or disruptive changes.

The gross descriptions of all reports were then reviewed and correlated with the microscopic findings. All cases in which the blind microscopic review had demonstrated severe myxoid changes were singled out and further examined.

Portions of normal valve tissue as well as of a surgically excised valve (B 23911) showing gross and microscopic evidence of myxoid change were processed for electron microscopic examination. Immediately after the tissue was obtained small pieces were

From the Departments of Pathology and Biophysics, The Hospital of the Good Samaritan Medical Center, Los Angeles, Calif.

Received for publication Oct 21, 1971.

Reprint requests to Dr William H Kern, Dept of Pathology, The Hospital of the Good Samaritan Medical Center, 1212 North St, Los Angeles, Calif 90017.

*Clinical Professor of Pathology, University of Southern California School of Medicine, Clarrisa Department of Pathology, The Hospital of the Good Samaritan Medical Center.

**Instructor in Surgery (Thoracic) of Southern California School of Medicine, Attending Staff, The Hospital of the Good Samaritan Medical Center.

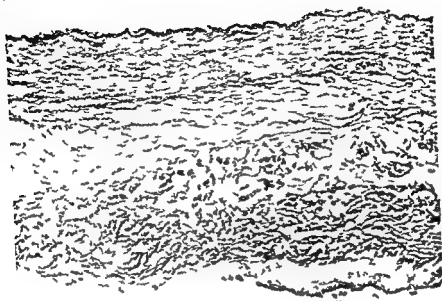


Fig. 2 Myxoid degeneration in noncalcified insufficient aortic cusp (Case 91) (Hematoxylin and eosin. Original magnification $\times 90$)

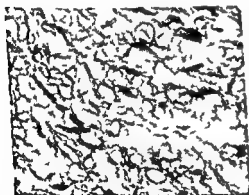


Fig. 3 Myxoid changes with prominent vacuolization in aortic cusp adjacent to extensive calcification, Case 29 (Hematoxylin and eosin. Original magnification $\times 500$)

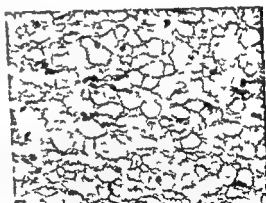


Fig. 4 Extensive myxoid changes in insufficient noncalcified mitral valve with elongated chordae (Case 202) (Hematoxylin and eosin. Original magnification $\times 500$)

Sixteen of these tissues were aortic cusps, sixteen were mitral valves, and two were tricuspid valves. Correlation with the gross descriptions after completion of the microscopic review indicated that in 14 of the 34 cases the valves contained extensive areas of calcification and were grossly considered to be characteristic of chronic rheumatic disease. The histologic appearance of the myxoid changes in these cases

as exemplified in Figs. 1 and 3 is identical with those observed in valve tissue showing myxoid change as the predominant pathologic pattern (Figs. 2 and 4).

The 20 cases of severe myxoid change in not significantly calcified presumably non-rheumatic valves are summarized in Table III. Some valves were moderately fibrosed but there was no significant scarring or evidence of stenosis and only one (case 61) con-



Fig. 1 Myxoid changes in noncalcified portions of aortic cusp tissue from case (No. 40) of calcific aortic stenosis and insufficiency (Hematoxylin and eosin. Original magnification $\times 90$)

Table II Myxoid changes in excised valve tissues (344 cases)

Tissues	Minimal/slight	Moderate	Severe	Total
Aortic valves (150)	51	42	16	109 (73%)
Mitral valves (202)	91	39	16	146 (73%)
Tricuspid valves (11)	2	3	2	7
Total	144	84	34	262

of the sectioned leaflet (Figs. 1 and 2) and occupied one third or more of the specimen. High power examination under the light microscope shows the prominent vacuolization (Figs. 3 and 4) with the associated disruption of the normal connective tissue architecture and an apparent relative increase in the ground substance. Alcian blue special stains demonstrate increased amounts of mucopolysaccharides. The histologic changes are quite similar to those observed in the cystic medial necrosis associated with Marfan's disease.

The electron microscopic examination reveals striking changes associated with this myxoid degeneration. The orderly pattern of fibrils in normal valve tissue is shown in Figures 5 and 7. The collagen fibrils are

arranged in the form of small bundles in an orderly parallel pattern and the characteristic cross banding is well demonstrated. In contrast, in valve tissue that undergoes myxoid degenerative change the fibrils occur singly in a disorderly arrangement (Fig. 6) and under higher power (Fig. 8) are seen to vary in length and thickness and are often tapered. Cross bandings are no longer recognizable and the extrafibrillar ground substance is of increased translucency and may be increased in amount. This correlates with the light microscopic appearance and the increase in mucopolysaccharides demonstrated by special stains.

Thirty four of the 344 cases reviewed showed myxoid degenerative changes which were considered to be severe and disruptive

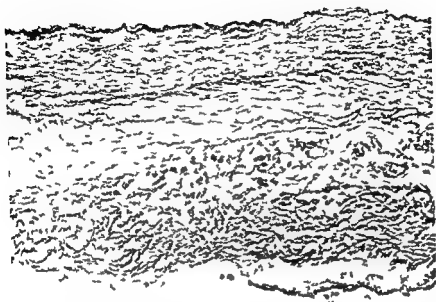


Fig 2 Myxoid degeneration in noncalcified insufficient aortic cusp Case 94 (Hematoxylin and eosin. Original magnification $\times 90$)

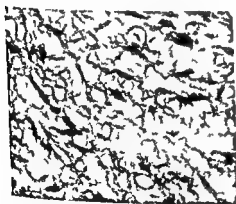


Fig 3 Myxoid changes with prominent vacuolization in aortic cusp adjacent to extensive calcification, Case 29 (Hematoxylin and eosin. Original magnification $\times 500$)

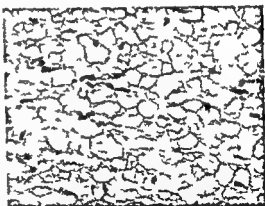


Fig 4 Extensive myxoid changes in insufficient noncalcified mitral valve with elongated chordae Case 20 (Hematoxylin and eosin. Original magnification $\times 500$)

Sixteen of these tissues were aortic cusps sixteen were mitral valves and two were tricuspid valves. Correlation with the gross descriptions after completion of the microscopic review indicated that in 14 of the 34 cases the valves contained extensive areas of calcification and were grossly considered to be characteristic of chronic rheumatic disease. The histologic appearance of the myxoid changes in these cases

as exemplified in Figs 1 and 3 is identical with those observed in valve tissue showing myxoid change as the predominant pathologic pattern (Figs 2 and 4)

The 20 cases of severe myxoid change in not significantly calcified presumably non-rheumatic valves are summarized in Table III. Some valves were moderately fibrosed but there was no significant scarring or evidence of stenosis and only one (case 61) con-

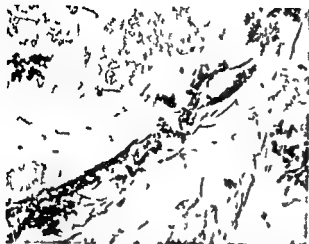


Fig. 5 Normal mitral valve leaflet. The collagen fibrils are arranged in regular bundles and are embedded in a homogeneous ground substance. Electron photomicrograph. Original magnification $\times 16,500$.

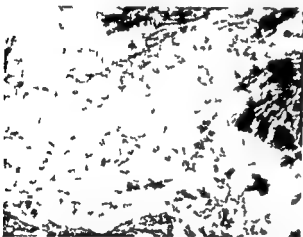


Fig. 6 Myxoid change characterized by a more translucent ground substance and by disruption and disordered arrangement of collagen fibrils. Electron photomicrograph. Original magnification $\times 16,500$.

trained microscopic foci of calcification. The original pathologic gross descriptions were variable but in 12 cases they stressed that the tissue was thin, delicate, flabby, translucent, or edematous. Myxoid changes were described microscopically in 15 of the 20 cases. Such changes were also originally noted in 7 of the 228 cases in which on review they were observed to be present but minimal or moderate in degree.

Sixteen of the patients were men and four were women. They ranged in age from 15 to 68 years with an average age of 42 years. This is approximately ten years younger than the average age for all cases reviewed.

Nineteen of the patients had insufficient

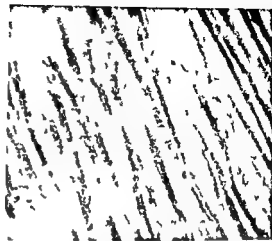


Fig. 7 High power electron photomicrograph of normal valve tissue showing collagen fibrils with distinct cross bandings in orderly arrangement. Electron photomicrograph. Original magnification $\times 108,000$.

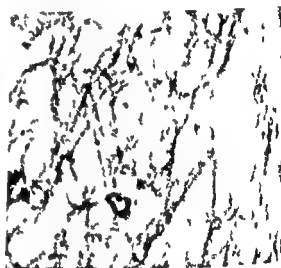


Fig. 8 Area of myxoid change with fragmentation and haphazard arrangement of collagen fibrils. Cross bandings are not demonstrable. Electron photomicrograph. Original magnification $\times 108,000$.

valves. One had an atrial septal defect and a cleft mitral valve. In four cases the surgeons found the chordae to be elongated and in one case ruptured. In another instance the chordae were shortened and in this as well as two other cases the surgical impression was that of a rheumatic lesion. Pathologically there was no evidence that this was the case. The postoperative course and follow up for 15 patients was satisfactory, the follow up period ranging up to six years. Two of the patients died in the immediate postoperative period and three others died three to five months after surgery, one due to a paravalvular leak.

Table III. Secondary myxoid changes in nontalcified nonrheumatic valves

Animal no.	Sex	Age (yrs)	Stigmata of Marfan's disease	Valve excised	Surgical findings	Postoperative condition length of follow-up
59	F	40	No	Aortic	AI post-rheumatic	Satisfactory 3 mos
61	M	21	Yes	Aortic	AI dilated annulus (?) SBE	Satisfactory 4 yrs.
89	F	38	No	Mitral	MI elongated chordae	Satisfactory 5 yrs.
94	M	24	No	Aortic	AI bicuspid valve	Satisfactory 1 yr
101	M	15	No	Aortic	AI post-rheumatic	Satisfactory 6 yrs.
106	M	52	No	Mitral	MI elongated chordae (?) SBE	Satisfactory 2 yrs.
114	M	51	No	Aortic	AI bicuspid valve	Died postoperatively
116	M	25	No	Tricuspid	TI dilated annulus severe pulmonary hypertension	Died postoperatively
148	M	27	No	Aortic	AI bicuspid valve	Satisfactory 2 yrs.
150	M	57	No	Tricuspid	TI dilated annulus	Satisfactory 2 yrs.
169	M	38	No	Aortic	AI post-rheumatic	Satisfactory 5 yrs
177	M	53	No	Aortic	AI SBE	Satisfactory 9 mos
185	F	59	No	Mitral	MI ruptured chordae	Satisfactory 3 yrs
192	F	68	No	Aortic	AI dilated annulus loss of valve substance	Satisfactory 2 yrs
196	M	60	No	Mitral	MI elongated chordae (?) Marfan's	Satisfactory 3 yr
202	M	49	No	Mitral	MI elongated chordae	Satisfactory died 5 mos postoperatively
204	M	27	No	Mitral	MI ostium primum repaired 2 years before	Satisfactory died 4 mos paravalvular leak
221	M	54	No	Mitral	MI post-rheumatic	Satisfactory 3 yrs
265	M	40	Yes	Aortic	AI Marfan's	Satisfactory died 3 mos postoperatively
336	M	25	No	Aortic	AI dilated annulus	Satisfactory 1 yr

Abbreviations: AI = aortic insufficiency; SBE = bicuspid aortic disease; MI = mitral insufficiency; TI = tricuspid insufficiency.

Two of the patients both men 21 and 50 years of age had aortic insufficiencies and clinical stigmas of Marfan's disease. In the remaining 18 patients there was no historical or clinical evidence of Marfan's disease or habitus.

Discussion

The findings reported in this study are based on a microscopic review of a larger number of consecutive surgically excised valve tissues than previously recorded in the literature. They illustrate that myxoid changes are a very common finding and are present at least to a slight degree in over two thirds of the cases examined. It is obvious that in most cases they do not represent a specific disease process. Pomerance and Whitney¹² also called attention to the frequency of these changes as incidental autopsy findings. They point out that these changes are the only clinically significant

degenerative changes of valves and that chronic valve disease associated with such changes is the commonest cause of heart failure in dogs. Myxoid degeneration on the other hand was not seen in the heart valves of aging rats.¹³ The incidence of severe or disruptive myxoid changes in 10 per cent of our surgical pathologic material corresponds to the findings of Frable⁴ who found similar lesions in 23 of 140 excised valves. Seven cases were true floppy valves. All of his cases occurred in men and involved aortic cusps. Our findings demonstrate that severe myxoid changes occur in mitral and tricuspid as well as in aortic valve tissue and in many of these cases they appear to be principally responsible for the valve insufficiency. In the mitral valve this may be associated with elongation of chordae. It is interesting to note that 5 of the 14 cases which were excluded from the principal study group because the

gross pathologic changes were characteristic of rheumatic disease also had elongated or ruptured chordae tendinae.

Subacute bacterial endocarditis was present or suspected in three of our cases, which fact is of interest since a predisposition to bacterial endocarditis has been previously reported.⁸

Table I shows a striking preponderance of men among patients undergoing aortic valve surgery. This is undoubtedly due to the higher incidence of calcific aortic stenosis and suggests that many of these cases are nonrheumatic. Females predominate in a ratio of two to one in the mitral valvectomy group. Most of the excised mitral valves show morphologic changes characteristic of rheumatic disease, possibly reflecting a slightly greater prevalence of rheumatic fever in females. Our review confirms that severe and clinically significant myxoid changes occur more frequently in men than in women (see Table III). This correlates with a greater number of involved aortic rather than involved mitral valves and may be related to the striking sex distribution of valvular disease in our surgical case material.

The demonstration that myxoid degeneration may occur alone as the principal pathologic change but that histologically identical changes may be associated with chronic rheumatic valvulitis is of particular interest. The similarity of the observed changes to those of cystic medionecrosis is striking and has been repeatedly noted.^{9,10,14} Several patients in other reported series had Marfan's disease^{1,9,10} and the inclusion of two patients with clinical findings of Marfan's disease in our series further suggests such an association. But even the severe myxoid changes associated with Marfan's disease cannot be distinguished objectively from equally severe changes that occur in chronic rheumatic valvulitis and presumably in other conditions. It does not therefore appear justifiable to consider all cases of extensive myxoid change as a variant of Marfan's disease. Despite statements in the literature that histologic examination of excised valve tissue is rarely helpful,¹⁵ careful routinely performed microscopic studies must be correlated with clinical, surgical, and gross findings in order to recognize

those cases in which severe myxoid change is unassociated with rheumatic or with other significant valvular disease and in which it has caused valvular insufficiency. These cases then can be recognized as being idiopathic. Some will be found associated with characteristic Marfan's disease whereas the majority are isolated lesions and may be considered a forme fruste of the same syndrome.¹¹ In view of the great frequency with which myxoid changes are being encountered, we concur with Pomerance and Whitney that at least the less severe changes are a tissue reaction which, like endocardial fibroelastic thickening, is the end result of many etiologic factors including both congenital and aging changes.⁸ That aging is probably not very important is indicated by the relatively low average age of 42 years for our group of patients.

The ultrastructural pattern of valve tissue undergoing myxoid change is of particular interest. Normal subendothelial valve tissue consists of fibrocytes, histiocytes and collagenous fibrils embedded in ground substance.¹⁶ The normal amorphous ground substance is optically homogeneous and since it consists largely of protein polysaccharides it stains metachromatically.¹⁷ The prominent metachromatic staining of myxoid lesions appears to indicate a relative increase of polysaccharides in the ground substance.^{9,9,10} This corresponds with the light microscopic appearance of prominent vacuoles (Figs 3 and 4). However it appears on examination of the electron photomicrographs that the ground substance is altered and loosened as well as possibly slightly increased in amount. The most striking change is the disorganization and degeneration of the fibrillar structures with loss of cross bandings. It is considered likely that this tissue breakdown and derangement are associated with qualitative changes in the ground substance that lead to changes in staining characteristics.

Summary

The histologic review of 344 consecutive surgically excised aortic, mitral and tricuspid valves demonstrated myxoid degenerative changes in 262 cases. In most cases these changes were minimal but in 34 instances they were severe or disruptive

In 14 instances this was associated with rheumatic valvulitis with marked calcification whereas in 20 cases the myxoid changes were the predominant finding. Sixteen of these 20 patients were men and four were women. The average age was 42 years, ten years less than that of all cases reviewed. Eleven aortic, seven mitral and two tricuspid valves were involved. All were insufficient. The histologic findings were consistent with Marfan's disease. Two of the 70 patients showed clinical stigmas of this syndrome. The clinical, surgical and morphologic correlation suggests that the lesion in this group of patients represents an idiopathic disease process but the morphology alone is nonspecific. Particularly lesser degrees of myxoid change appear to be a tissue reaction to a variety of etiologic factors. The ultrastructural appearance is characterized by a disruption of the fibrillar pattern, qualitative changes with loss of cross bandings in collagen fibrils and a relative increase and greater translucency of the ground substance.

The authors wish to thank Dr. Gerald B. Dermer for the preparation of the electron photomicrographs and Dr. Richard A. Nolan for his participation in the preparation and case selections.

REFERENCES

1. Aslam, P. A., Eastridge, C. E., Bernhardt, H. and Pace, J. W. Myxomatous degeneration of cardiac valves. *Chest* 57:535, 1970.
2. Bitar, N. and Sosa, J. A. The billowing mitral valve leaflet. Report on fourteen patients. *Circulation* 38:163, 1968.
3. Castleman, H. Case records of Massachusetts General Hospital. *N. Engl. J. Med.* 277:92, 1967.

4. Frable, W. J. Mucinous degeneration of the cardiac valves. The floppy valve syndrome. *J. Thorac. Cardiovasc. Surg.* 58:62, 1969.
5. Hudson, R. E. B. Cardiovascular pathology, vol. 3. Baltimore, 1970. Williams & Wilkins Company, pp. 342-347.
6. McCarthy, L. J. and Wolf, P. L. Mucoid degeneration of heart valves: blue valve syndrome. *Am. J. Clin. Pathol.* 51:852, 1970.
7. Pomerance, A. Aging changes in human heart valves. *Br. Heart J.* 29:222, 1967.
8. Pomerance, A. Ballooning deformity (mucoid degeneration) of atrioventricular valves. *Br. Heart J.* 31:343, 1969.
9. Read, R. C. and Thal, V. P. Surgical experience with symptomatic myxomatous valvular transformation (The floppy valve syndrome). *Surgery* 59:173, 1966.
10. Read, R. C., Thal, A. P. and Wendt, V. E. Symptomatic valvular myxomatous transformation (The floppy valve syndrome). *Circulation* 30:897, 1965.
11. Read, R. C., White, H. J. and Palacios, E. Floppy valve syndrome—a possible expression of pituitary and mucopolysaccharide dysfunction. *Surg. Clin. North Am.* 46:1427, 1967.
12. Pomerance, A. and Whitney, J. C. Heart valve changes common to man and dog. Comparative study. *Cardiovasc. Res.* 4:61, 1970.
13. Nakao, K., Mao, P., Ghidoui, J. and Angrist, A. An electron microscopic study of the aging process in the rat heart valve. *J. Gerontol.* 21:171, 1966.
14. Hudson, R. E. B. Cardiovascular pathology, vol. 1. Baltimore, 1965. Williams & Wilkins Company, p. 522.
15. Roberts, W. C. and Morrow, A. G. Cardiac valves and the surgical pathologist. *Arch. Pathol.* 82:309, 1966.
16. Kuhnelt, W. Zur Feinstruktur der Herzklappen. *Ergeb. Rheumaforsch.* 2:10, 1966.
17. Bloom, W. and Fawcett, D. W. A textbook of histology, 9th Ed. Philadelphia, 1968. W. B. Saunders Co., pp. 381, 382 and pp. 131, 141.

Vectorcardiographic and electrocardiographic differentiation between cor pulmonale and anterior wall myocardial infarction

Yoshihiko Watanabe, M D

Kenji Nishijima, M D

Harold Richman, M D

Ernst Simonson, M D

Minneapolis, Minn

The vectorcardiographic differentiation between anterior myocardial infarction (MI) and chronic obstructive pulmonary (lung) disease (COLD) has long been recognized as a difficult diagnostic problem in that both conditions are characterized by reduced or absent anteriorly directed initial forces. It is surprising, therefore, that only one quantitative investigation with the purpose of improving the differentiation has been reported by Ishikawa and associates.¹ In their sample of 1002 patients with myocardial infarction (MI) and 405 patients with pulmonary emphysema (PE) over 300 vectorial and scalar (I rank leads X, Y, and Z) items were measured with the aid of electronic computers. A significant improvement in the separation of these two conditions was achieved when multivariate statistical analysis including multidimensional (arithmetic) vectors was utilized. By means of a combination of a relatively small number of items which could be measured manually the original 50 per cent of emphysema records which could have been erroneously interpreted as MI was reduced to 16 per cent. More com-

plex multivariate analysis with a larger number of items resulted in further improvement with a residual error of 13 per cent.

In view of the relatively limited information available we felt that another quantitative investigation of this important problem would be justified. Our sample of MI and COLD patients is smaller than that of the Ishikawa group. However, the selection of MI patients was based on detailed autopsy analysis and the localization of MI is more precise. Ishikawa and co-workers used only the Frank leads. We used Frank leads as well as the conventional lead electrocardiogram (ECG) so that the diagnostic performance of the two lead systems could be compared. The number of items analyzed, being limited to those which could be measured manually, was much smaller than in Ishikawa's study.

Materials and method

The sample consisted of 52 patients with COLD (age range 42 to 79 years mean age 56.0) and 35 with anterior myocardial infarction (MI) (age range 35 to 78 years

From the Mount Sinai Hospital and the Veterans Administration Hospital, Minneapolis, Minn.

Supported by Grant HE 11325 from the National Heart and Lung Institute.

Received for publication Oct. 25, 1971.

Requests for reprints to: Ernst Simonson, M.D., Mount Sinai Hospital, 2215 Park Ave., Minneapolis, Minn. 55404.

Vol 24
No 2

Table I

Scalar and vectorial items analyzed—Frank leads	
Scalar \backslash Y Z lead Q R S T	12 items
Vectors \backslash Y Z coordinate of QRS 70 msec 5 msec max +20 msec and maximal T	15 items
Combination $R_x + R_z$ $S_x/(S_x + R_x)$ $Q_x/(Q_x + R_x)$ $S_x + Q_x$	4 items
Time interval Q_x Q_z Q_x QRS and peak time	5 items
Total	36 items

Items analyzed in 9 lead ECG (standard leads I, II, III, aVR, aVL, aVF, V1, V4, V6)

Q R S amplitude in 9 leads	27 items
P amplitude in Leads I II III and aVR	4 items
Q duration in 9 leads	9 items
S R, Q/R in 9 lead	18 items
Peak to peak QRS amplitude in 9 leads	9 items
QRS duration, frontal axis $R_{V_6} + S_{V_1}$	4 items
Total	71 items

Table II Categories of vectorial and scalar items with high correlations within each category and little correlation between the different categories

Spatial	Scalar
(1) 20 msec \backslash 75 msec \backslash maximal QRS -20 msec \backslash maximal T _x -20 msec \backslash maximal QRS _y	Qx amplitude Qx amplitude Rx amplitude Sx amplitude Tx amplitude Sy amplitude Ry amplitude
(2) maximal QRS _z maximal T _z	Rz amplitude Tz amplitude
(3) 70 msec Z 25 msec f	Qz amplitude Qz duration
(4) 20 msec \backslash 25 msec \backslash	Qy amplitude Qy duration
(5) QRS duration peak time	

tracings (paper speed 20 cm per second) were analyzed. In the upper part of Table I the 36 items measured in the Frank leads are listed and in the lower part the 71 items measured in the conventional nine lead ECG (augmented unipolar leads were not utilized except for P in aVR).

The general purpose of the statistical analysis was determination of the minimum number of items (single or combinations) for the best separation of MI and COLD. As a first step the means and the standard deviations were calculated for each item in both groups (COLD and MI). As a second step to avoid a redundancy of information the correlation coefficients between the 36 Frank lead items were determined in COLD and MI amounting to 630 correlations* and the items with a high correlation coefficient were classified into the same group. Then the items were clustered into five independent categories as shown in Table II. The correlation among the items in each category is high but there is little correlation between the items of the different categories. The Student t test was carried out for the two groups. Four items with the highest t value in each category were chosen as parameters for the best discrimination of COLD and anterior MI

mean age 57.5) who had been admitted to Minneapolis Veterans Administration Hospital. COLD cases were classified as moderate to severe on the basis of clinical and radiologic findings and pulmonary function tests. The 35 cases of infarction were verified by autopsy findings. A scar of the myocardium extending at least 2.0 cm in one dimension and/or acute degenerative necrotic changes were taken as criteria for MI. Generalized myocardial fibrosis was excluded. Post mortem examination of the hearts was performed as previously described.² Five longitudinal and three transverse sections yielded 15 areas for MI localization. Ten patients had pure anterior infarction. 11 had anteroseptal and lateral MI. 9 had anterior and inferior MI. 5 had extensive infarction with an involvement of the anteroseptal, inferior and lateral wall. The corrected orthogonal vectorcardiograms (Frank lead system) were recorded with an Electronics for Medicine DR 8 photographic recorder. The electrodes were placed at the level of the fourth intercostal space in the supine position. The frontal, horizontal and left sagittal planar loop projections as well as X, Y and Z scalar

Table IIIA Means and standard deviations (SD) of scalar and vectorial items for COLD and MI patients with statistical significance of differences (t test)—Frank leads

Items	COLD		MI		t
	Mean	SD	Mean	SD	
Max spatial QRS	λ 0.037 mv	0.525	0.558	0.676	4.20†
	z 0.264	0.365	0.724	0.196	3.70*
Max spatial T	λ 0.063	0.116	-0.014	0.110	3.12*
	y 0.241	0.141	-0.004	0.154	7.66†
20	z -0.124	0.153	0.160	0.245	6.09†
25	z -0.087	0.251	0.354	0.353	6.11†
Scalar amplitude	Q 0.012 mv	0.045	0.085	0.176	3.78
λ	R 0.362	0.253	0.649	0.462	3.35†
	S 0.285	0.302	0.153	0.150	2.11
	T 0.076	0.091	-0.008	0.124	3.64†
y	T 0.192	0.096	0.000	0.170	6.01†
z	R 0.489	0.252	0.994	0.397	6.33†
$R\lambda + R_z$	0.851	0.357	1.643	0.681	6.65†
$S\lambda/(R\lambda + S\lambda)$	0.417	0.287	0.245	0.264	7.82
$Qz/(Qz + R_z)$	0.313	0.167	0.147	0.162	4.52†
QRS duration	93.56 msec	20.48	105.49	13.92	3.23*
Qx duration	3.17	7.92	12.47	13.45	3.64†
Qz duration	30.19	14.31	14.26	10.09	5.10†

*p < 0.01

†p < 0.001

These four items were selected: $R\lambda + R_z$, 25 msec z QRS duration and $S\lambda/(S\lambda + R\lambda)$. Finally, the discrimination of the two groups was performed with a 'weighted vector difference' method[†].

The respective distances of each subject from the arithmetic mean vectors of COLD and MI were obtained using a weighting factor inverse to the standard deviation. Therefore, the distance corresponded with the probability density of a subject to be classified in COLD or MI.

The statistical evaluations of the data were performed by the use of a CDC 3300 computer.

Results

I Orthogonal (Frank) leads Table IIIA shows the means and standard deviations (SD) for COLD and MI groups with highly significant mean differences between the two groups (t test).

When grouped according to the correlation coefficient, redundant information was reduced and a small number of effective

parameters was obtained (see Table IV).

In each category the following items were selected for best discrimination between COLD and MI: (1) amplitude of wave in Lead λ ($R\lambda$) ($t = 3.35$), (2) amplitude of R wave in Lead Z (R_z) ($t = 6.33$), (3) Z component of spatial 25 msec vector (25 msec z) ($t = 6.77$), (4) QRS duration ($t = 3.23$).

Since the combination of $R\lambda$ and R_z gave a higher t value (6.68) than its individual items, $R\lambda + R_z$ was selected as single parameter for the discrimination.

$S\lambda/(R\lambda + S\lambda)$ was utilized additionally because of its usefulness in the discrimination of COLD patients from normal subjects. Table IV (upper part) shows the best discriminating values with percentage distribution of COLD and MI. In the individual use of the above parameters

$R\lambda + R_z$ resulted in 75 per cent of correct diagnoses in COLD patients and 93 per cent in MI patients. 25 msec z in S1 and 77 per cent respectively and QRS duration in 85 and 57 per cent, respectively. The combination of $R\lambda + R_z$ and 25 msec z identified correctly 83 per

*Frank leads.

†See Appendix I for details.

Table IIIB Means and standard deviations (SD) of conventional ECG items for COLD and VI patients with statistical significance of differences (t test)

Items	COLD		VI		t
	Mean	SD	Mean	SD	
RI	0.281	0.156	0.556	0.382	4.66
SV ₁	0.499	0.419	1.158	0.941	4.45
SV ₂	0.942	0.678	1.643	1.095	3.69
QV ₁	0.007	0.031	0.552	1.002	3.93
RV ₁	0.818	0.409	0.457	0.539	4.15
QV ₂	0.003	0.027	0.217	0.431	3.50
P ₁₁	0.188	0.068	0.126	0.080	3.88
P ₁₂	0.145	0.012	0.086	0.016	3.61
PaVF	0.168	0.077	0.103	0.074	3.92
QDV ₁	1.10	4.2	23.4	37.0	4.33
QDV ₂	0.7	2.8	19.9	31.9	4.33
QDV ₃	1.5	4.2	19.7	30.2	4.30
QRSd	83.1	8.6	94.3	8.9	5.87
S/R in V ₁	5.1	5.2	14.5	17.9	3.56
V ₁	3.6	3.0	17.7	23.8	4.23
V ₂	2.5	2.0	11.8	17.0	3.90
V ₃	1.1	0.9	5.4	8.9	3.43
Total deflection I	0.397	0.163	0.647	0.375	4.25
V ₁	0.744	0.368	1.530	0.846	5.93
V ₂	1.303	0.64	2.272	0.827	5.61
V ₃	1.429	0.690	2.217	0.812	4.86
RV ₁ + SV ₁	1.512	0.562	2.307	1.346	3.803
RV ₂ + SV ₂	1.319	0.546	2.363	1.318	5.111

*p < 0.001

cent of COLD cases and 88 per cent of VI cases (Table V). The combination of Rx + Rz 25 msec z and QRS duration identified correctly 118 per cent of COLD and 88 per cent of VI cases. The addition of S₁/(Rx + Sx) resulted in correct identification of 88 per cent of COLD and 91 per cent of VI cases.

As an additional estimative method a linear discriminant function⁶ was utilized. The coefficients of the four parameters are listed in Table VI (left Frank leads right conventional lead) and the percentage of correct classification was estimated as 89 per cent using Mahalanobis distance (Fig 1).⁶ This result showed approximately the same diagnostic accuracy as the weighted vector difference method.

II Conventional leads Table IIIB lists the means and standard deviations of all items with highly significant differences (p = < 0.001) between the COLD and VI groups. In a procedure similar to the evaluation of the orthogonal Frank leads four

items were selected for differentiation between the COLD and VI groups and listed in the lower part of Table IV. RV₁ + SV₁* (corresponding to Rx + Rz), RV₂ (corresponding to 25 msec z), QRS duration and PaVF.

The identification of the COLD group was quite similar for RV₁ + SV₁ and Rx + Rz but better for the 25 msec anterior vector coordinate than for RV₂, probably because it is more anteriorly directed. The correct identification of 60 per cent by means of PaVF was surprisingly low. The correct identification of the VI group ranged from 71 to 77 per cent in the four items.

The differentiation between COLD and VI groups by means of combinations of conventional ECG items is listed in the lower part of Table V. The correct identification of 81 per cent of COLD patients

*This item was selected because of the directional similarity of Rx + Rz.

Table IV Recognition rate of COLD and MI by individual parameters in number and percent of

Frank leads				
Disease	$Rx + Rz$	25 msec	QRS duration	$Sx/(Rx + Sz)$
COLD (52)	39 (75%)	42 (81%)	44 (85%)	50 (58%)
MI (35)	29 (83%)	27 (77%)	20 (57%)	27 (77%)
Best discriminating value	1.12 mv	0.10 mv	100.7 msec	0.33 mv

Table V Recognition rate by various combinations of parameters

Frank leads			
Disease	$Rx + Rz$ + 25 msec	$Rx + Rz$ + 25 msec + QRS duration	$Rx + Rz$ + 25 msec + QRS duration + $Sx/(Rx + Sz)$
COLD (52)	43 (83%)	46 (88%)	46 (88%)
MI (35)	31 (88%)	31 (88%)	31 (91%)

with two combinations $Rx + Sz$ plus QRSd, is quite satisfactory and is not improved by adding other items. In contrast the identification of MI patients is improved by adding Rx and $P+VF$ to 94 and 97 per cent, respectively and is excellent.

The results obtained with using the linear discriminant functions are listed in Table VI, right part.

Discussion

There were a considerable number of COLD patients with reduced or absent initial anteriorly directed QRS forces (13 of 52 patients [25%]). As emphasized by Ishikawa and associates¹ these are frequently misdiagnosed as MI in routine clinical vectorcardiography or electrocardiography. A reasonably good discrimination using only two parameters, $Rx + Rz$ and "25 msec z," was obtained because as previously noted¹ a reduction in amplitude

of Rx and Rz occurred only in cases of COLD. The discriminative point of $Rx + Rz$ between MI and COLD of 1.12 mv would indicate a recognition rate of 83 per cent in cases of MI and 75 per cent in instances of COLD respectively. However, the Z component of the spatial 25 msec vector (25 msec z) was a still better parameter to differentiate the two entities. Utilizing 0.10 as a discriminative threshold a correct identification of 81 per cent of cases of COLD and 77 per cent of cases of MI (Table IV) was possible.

Many investigators have used the Q amplitude and/or duration or Q/R ratios in lead Z for discrimination although the distribution of the Q amplitude or Q/R ratios was quite different from a normal distribution. On the other hand, in our material the distribution of "25 msec z" was a fairly normal distribution and therefore superior for statistical analysis. The distribution of 25 msec z was wider and

and

Conventional ECG leads

Disease	$R_{I_1} + S_{I_1}$	RV_4	QRS_d	$PaVF$
LD (52)	38 (73%)	34 (65%)	44 (85%)	31 (60%)
(35)	27 (71%)	26 (74%)	27 (77%)	25 (71%)
discriminating value	1.62 mv	0.10 mv	88.1 msec	0.13 mv

Conventional ECG leads

Disease	$R_{I_1} + S_{I_1}$ + QRS_d	$R_{I_1} + S_{I_1}$ + QRS_d + R_{I_4}	$R_{I_1} + S_{I_1}$ + QRS_d + RV_4 + $PaVF$
D (5%)	42 (81%)	42 (81%)	40 (79%)
(35)	31 (89%)	33 (94%)	34 (97%)

was deviated more posteriorly in cases of MI than in instances of COLD.

QRS duration improved the diagnostic separation only slightly because of the overlapping distribution of this parameter in both groups. The cut off point was 100.7 msec.

$S_x/(R_x + S_x)$ was one of the best discriminators between COLD and Normal but less effective for discrimination of COLD from MI. However in combination with other items it improved only slightly the discrimination (Table IV).

As shown in Table V use of the combination of R_x and R_z , QRS duration, 25 msec or more, and $S_x/(S_x + R_x)$ i.e. four items easily manually determined resulted in correct identification of 88 per cent of COLD patients and 91 per cent of MI patients which compares favorably with results of the Ishikawa group. Comparing the diagnostic performance of orthogonal Frank leads and conventional ECG leads

the Frank leads are somewhat superior for correct recognition of COLD patients (88 vs 81 per cent) while the conventional leads are somewhat superior for correct identification of MI (97 vs 91 per cent). The differences however are not very great. Examples for clinical application of the weighted vector differences are given in Appendix II. It would appear that linear discriminant function analysis significantly improves the differentiation of MI from COLD. However there is little difference in reliability between Frank lead and conventional ECG lead analysis.

Summary

The vectorcardiographic differentiation between anterior wall myocardial infarction (MI) subjects (35 patients selected from detailed autopsy data) and 52 patients with chronic obstructive lung disease (COLD) was considerably improved by multivariate statistical analysis. Thirty six scalar

Table VI Linear discriminant function between COLD and MI*

Frank leads		Conventional ECG leads	
Parameters	Coefficients	Parameters	Coefficients
$R_x + R_z$	-3.34	$RV_4 + SV_1$	-1.57
25 msec. z	-5.55	RV_4	+3.44
QRS duration	-0.0389	QRSd	-0.116
$S_x/(S_x + R_x)$	-0.0359	PaVF	+13.4
Constant	+8.82	Constant	+9.03
Mahalanobis distance	5.66	Mahalanobis distance	5.35
L	1.19	L	1.16

*The coefficients are to be multiplied with values of the combined parameters listed in the first column and added. If the sum is positive it indicates MI; if negative it indicates COLD as illustrated in the scatter diagram of Fig. 1.

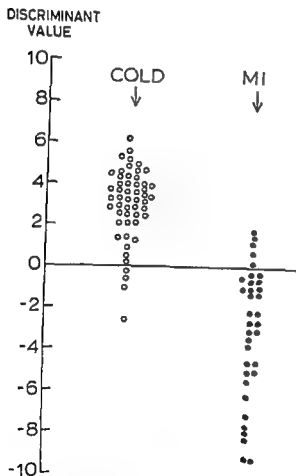


Fig. 1 See footnote of Table VI

items, all measured manually were analyzed. The combination of only four items, $R_x + R_z$, 25 msec. z component QRS duration and $S_x/(S_x + R_x)$ resulted in correct identification of 88 per cent of patients with COLD and 91 per cent of

patients with MI. Multivariate analysis of conventional ECG items differentiated between the two groups equally well, somewhat superior for MI with correct identification of 97 per cent of cases for combination of four items and somewhat inferior for COLD with correct identification of 81 per cent of instances with a combination of two items ($RV_4 + SV_1$ plus QRS interval).

REFERENCES

1. Ishikawa K, Eddleman E E and Pipberger H V. Electrocardiograms in pulmonary embolism mimicking myocardial infarction. *Med Ann D C* 39:20, 1970.
2. Richman H, Yokoi M, Gleason D, Nishiyama K and Simonson E. Reliability of the vector cardiographic diagnosis of myocardial infarction. *Vectorcardiography 2: Proceedings of the XI International Symposium on Vectorcardiography 1970*. Amsterdam 1971. North Holland Pub Co.
3. Simonson E, Nishiyama K, Khalafalla A, Richman H, MacDonald F and Yokoi M. Vectorcardiogram, thoracic impedance and pulmonary functions in patients with chronic obstructive lung disease and healthy men. *Vectorcardiography 2: Proceedings of the XI International Symposium on Vectorcardiography 1970*. Amsterdam 1971. North Holland Pub Co.
4. Klingemann J and Pipberger H V. Computer classifications of electrocardiograms: computers and biomedical research, vol. 1. New York 1967. Academic Press Inc. p. 117.
5. Sebestyen G S. Decision making process in pattern recognition. New York 1967. The Macmillan Co. Publishers.
6. Anderson T W. An introduction to multivariate statistical analysis. New York 1958. John Wiley & Sons Inc.

Appendix I

Weighted vector differences Let

$$d(p, \mu^A) = \sqrt{\sum_{i=1}^N W_i^A (p_i - \mu_i^A)^2}$$

$$d(p, \mu^B) = \sqrt{\sum_{i=1}^N W_i^B (p_i - \mu_i^B)^2}$$

where

p_i = i^{th} component of unclassified point
 μ_i^A = i^{th} component of mean value from Group A
 μ_i^B = i^{th} component of mean value from Group B
 N = number of components
 W_i^A = weights inversely proportional to the standard deviation of the point p_i in Group A
 W_i^B = weights inversely proportional to the standard deviation of the point p_i in Group B

We classify $p \in A$ if $d(p, \mu^A) < d(p, \mu^B)$
 $p \in B$ if $d(p, \mu^B) < d(p, \mu^A)$

Appendix II

Table A Examples for clinical application of linear discriminant function

Parameters	Coefficients
Rx + Rx	-3.344
25 msec. z	-5.546
QRSd	-0.039
Sx/(Sx + Rx)	0.036
Constant	8.824

Example 1

PATIENT NO. 1 FROM COLD GROUP

$$\begin{aligned} & -3.344 \times 0.799 - 5.546 \times 0.029 \\ & -0.039 \times 23.0 + 0.036 \times 0.562 \\ & + 8.824 = 2.218 \end{aligned}$$

Example 2

PATIENT NO. 46 FROM MI GROUP

$$\begin{aligned} & -3.344 \times 1.429 - 5.546 \times 0.337 \\ & -0.039 \times 100.0 + 0.036 \times 0.072 \\ & + 8.824 = -1.723 \end{aligned}$$

Table VI Linear discriminant function between COLD and MI*

Frank leads		Conventional ECG leads	
Parameters	Coefficients	Parameters	Coefficients
'Rx + Rz	-3.34	RV ₁ + SV ₁	-1.57
25 msec z	-5.55	RV ₄	+3.44
'QRS duration	-0.0389	QRSd	-0.116
'Sx/(Sx + Rx)	-0.0359	PaVi	+13.4
Constant	+8.82	Constant	+9.03
Mahalanobis distance	5.66	Mahalanobis distance	5.35
L	1.19	L	1.16

*The coefficients are to be multiplied with values of the combined parameters listed in the first column and added. If the sum is negative it indicates MI; if positive it indicates COLD as illustrated in the scatter diagram of Fig. 1.

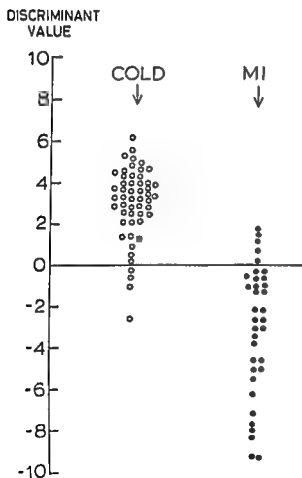


Fig. 1 See footnote of Table VI

items, all measured manually, were analyzed. The combination of only four items (Rx + Rz, 25 msec z component, QRS duration and Sx/(Sx + Rx)) resulted in correct identification of 88 per cent of patients with COLD and 91 per cent of

patients with MI. Multivariate analysis of conventional ECG items differentiated between the two groups equally well, somewhat superior for MI with correct identification of 97 per cent of cases for combination of four items, and somewhat inferior for COLD with correct identification of 81 per cent of instances with a combination of two items (RV₁ + SV₁ plus QRS interval).

REFERENCES

1. Ishikawa K, Eddleman E E and Pipberger H V. Electrocardiograms in pulmonary emphysema mimicking myocardial infarction. *Med Ann D C* 39:20, 1970.
2. Richman H, Yokoi M, Gleason D, Nishijima K and Simonson L. Reliability of the vector cardiographic diagnosis of myocardial infarction. *Vectorcardiography 2: Proceedings of the XI International Symposium on Vectorcardiography 1970*. Amsterdam 1971. North Holland Pub Co.
3. Simonson E, Nishijima K, Khalafalla A, Richman H, MacDonald F and Yokoi M. Vectorcardiogram, thoracic impedance and pulmonary functions in patients with chronic obstructive lung disease and healthy men. *Vectorcardiography 2: Proceedings of the XI International Symposium on Vectorcardiography 1970*. Amsterdam 1971. North Holland Pub Co.
4. Klingenstein J and Pipberger H V. Computer classifications of electrocardiograms: computers and biomedical research, vol. 1. New York 1967. Academic Press Inc. p. 117.
5. Sebestyen G S. Decision making process in pattern recognition. New York 1962. The Macmillan Co. Publishers.
6. Anderson T W. An introduction to multivariate statistical analysis. New York 1958. John Wiley & Sons Inc.

mal pair recorded a high right atrial (HRA) electrogram. In addition a bipolar catheter* was introduced into another antecubital vein and advanced to the right ventricular apex or outflow tract for ventricular pacing. During all stimulation sequences the surface electrocardiogram (ECG) electrograms and time lines generated at intervals of 10 and 100 msec were displayed on a multichannel switched beam oscilloscope† and recorded via a universal matching amplifier‡ onto magnetic tape. When the gain of the matching amplifier was adjusted the recording of the His potentials could be enhanced without overloading the tape recording assembly. Clipping of the ventricular electrogram resulted from this arrangement. Standard ECG Leads I, II, V₁ and V₆ were simultaneously recorded on a Sanborn 4560 recorder‡.

The refractoriness of various components of the AV conducting system (AVCS) was determined using the extrastimulus method^{10,12}. The bipolar atrial electrogram was electronically counted utilizing a specially designed digital stimulator§ allowing a premature atrial depolarization (A₂) to be introduced at variable intervals after every eighth sinus depolarization (A₁). The stimulus was a cathodal rectangular wave of 15 msec duration delivered at 7 to 3 times diastolic threshold. The prematurity of the stimulus was progressively decreased by 5 to 10 msec intervals until atrial refractoriness was encountered. In three of the seven patients the sequence of premature atrial stimulation was repeated at rates faster than the sinus rate. The basic drive following the premature beat was omitted to observe the effect of the premature beat. The following definitions were used and their intervals recorded.

Atrioventricular conduction system (AVCS) Includes the atrium specialized intra-atrial tracts, AV node, bundle of His, the three fascicular divisions of the bundle of His and Purkinje network.

Ventricular specialized conducting system (VSCS) A subdivision of the above term which includes the bundle of His

and all specialized conducting tissue distal to it.

Effective refractory period (ERP) of the AVCS The shortest test A₁ A₂ interval at which the premature atrial response still conducts to the ventricle.

Effective refractory period (ERP) of the VSCS The shortest interval between two His depolarizations (H₁ H₂) at which H₂ still propagates to the ventricle.

Functional refractory period (FRP) of the AVCS The minimum interval between two successive ventricular responses both propagated from the atrium (A₁ A₂).

Functional refractory period (FRP) of the VSCS The shortest H₁ H₂ interval between two successive His bundle responses both propagated from the atrium.

All equipment was suitably grounded and isolated. All patients tolerated the procedure without complications.

Results

The refractoriness of the various parts of the AVCS was determined in 50 patients using the extra stimulus method. The most common site of block of premature atrial impulses and hence the structure with the longest effective refractory period (LRP) was the AV node. However in seven patients block of premature atrial impulses occurred below the bundle of His. All were men between the ages of 45 and 66. Patients 1 and 3 had clinical histories of angina pectoris. Patient 7 had myotonic dystrophy. The remainder were found to have no evidence of heart disease. None of the seven was receiving medication prior to the study. Table I lists the functional properties of the AVCS in these seven patients. In all patients the ERP of the VSCS during sinus rhythm or slow basic cycle length was prolonged as compared to a group of normal subjects. These patients were identified at the time of study and further evaluation was performed to determine whether the AVR was located within the ventricular muscle or within the VSCS. This was accomplished by connecting the output of the stimulator, using low milliamperage to a pacing catheter located in the right ventricular apex (five

* U.S. Catheter & Instrument Corp., Glen Falls, N.Y.
† Electro-Medical Electronics, Inc., Elmsford, N.Y.
‡ Hewlett-Packard Co., Paramus, N.Y.
§ IBM Electro-Medical Division, Elmsford, N.Y.

Localization of an area of maximum refractoriness or "gate" in the ventricular specialized conduction system in man

John J. Gallagher, MD*

Anthony N. Damato, MD**

P. Jacob Varghese, MD***

Sun H. Lau, MD****

Staten Island, N. Y.

The AV node is usually the area demonstrating maximum refractoriness in man and is such might be called a gate. However, in approximately 10 per cent of patients (including normal subjects) and almost invariably in patients with LBBB¹ block of premature impulses occurs at some level distal to the bundle of His.

Previous experimental studies have shown that action potential duration progressively increases from the bundle of His distally toward the Purkinje fiber network^{2,3} and then diminishes in the transition from Purkinje cells to muscle.^{4,5} Myerburg and associates^{6,7} subsequently have demonstrated by microelectrode techniques an area of maximum refractoriness (AMR) or 'gate' just proximal to the termination of free running Purkinje fibers in muscle at the site of maximum action potential duration.

The AMR has not been previously demonstrated in those patients in whom block of premature atrial beats occurs distal to the bundle of His.

In the present study an attempt was made to localize this AMR more precisely in the human heart.

Methods

Right heart catheterization was performed in the postabsorptive, nonsedated state. A signed consent was obtained from all patients. Using a tripolar electrode catheter† introduced percutaneously into a femoral vein His bundle recordings were obtained according to methods previously described.⁸ In addition a quadripolar catheter‡ was introduced into an antecubital vein and positioned fluoroscopically against the lateral wall of the high right atrium. The distal pair of electrodes was used for atrial stimulation while the proximal

From the Cardiopulmonary Laboratory, United States Public Health Service Hospital, Staten Island, N. Y. This work was supported in part by the Federal Health Program Service, United States Public Health Service Project #71-1, National Heart and Lung Institute, Projects HE-11829 and HE-12536.

Received for publication Nov. 5, 1971.

Reprint requests to John J. Gallagher, M.D., Cardiopulmonary Laboratory, United States Public Health Service Hospital, Staten Island, N. Y. 10314.

*Research Associate, Cardiovascular Research, United States Public Health Service Hospital, Staten Island, N. Y.

**Chief, Cardiovascular Research, United States Public Health Service Hospital, Staten Island, N. Y.

***Visiting Scientist, Cardiovascular Research, United States Public Health Service Hospital, Staten Island, N. Y.

****Deputy Chief, Cardiovascular Research, United States Public Health Service Hospital, Staten Island, N. Y.

†U.S. Catheter & Instrument Corp., Glens Falls, N. Y.

Atrial node		VSCS ERP	H ₁ V	Δ	Ventricular pacing site	Ventricle refractory (H ₁ V)	Atrium refractory (A ₁ S)
FRP	ERP						
430	300	(520) 410	470	40	Apex	410	360
360	310	360	†	—	—	—	300
350	210	340	†	—	—	—	210
490	470	540	395	145	Outflow	345	390
480	400	480	395	85	Outflow	345	375
450	310	530	415	115	Outflow	—	290
430	410	460	430	30	Apex	—	390
440	360	440	†	—	—	—	340
300	210	360	330	30	Apex	330	240
385	325	410	335	75	Apex	325	290
610	450	680	460	220	Apex	400	220

Diff. = Difference between ERP of the VSCS and the H₁ V interval.
 4-8 = A measure of trial of activation. The longer the interval, the more pronounced the effect of the stimulus (S) fails to depolarize the atrium.
 SCL = Sinus cycle length.
 BCL = Basic cycle length (paced).
 LAF = Left atrio-fascicular (bifascicular) block.
 RBBB = Right bundle branch block.
 LBBB = Left bundle branch block.
 Study limited by trial refractoriness. No impulse block observed with bundle of His.

retrograde activation of the bundle of His and atria. This indicates that the area(s) of the VSCS which was maximally refractory and thereby prevented antegrade conduction to the ventricles (panel B H₁ H₂ interval = 515 msec) was less refractory at the time the retrograde ventricular impulse activated this region and consequently could permit retrograde conduction to the bundle of His (panel C H₁ H' = 570 msec). This can be explained by the fact that when the ventricles are pre-excited ventricular activation initially begins by muscle-to-muscle depolarization. A few milliseconds later (undetermined) the impulse enters the VSCS. This slight delay causes the retrograde impulse to reach the AVR at a time later in the cardiac cycle when it is less refractory. This explanation is supported by the fact that the interval from the onset of ventricular depolarization (V) to the retrograde His deflection (H) measures 150 msec which exceeds by 85

msec the longest H V interval which was obtained (panel A H₁ V₂ = 70 msec) just prior to failure of antegrade conduction to the ventricle (panel B).

Fig 3 taken from the same patient demonstrates a phenomenon which might be interpreted as an AMR or gate during retrograde conduction. In panel A a premature ventricular response (V) is elicited at an H₁ V interval of 420 msec resulting in delayed retrograde activation of the bundle of His and atria. There is a fully compensatory pause following the induced ventricular beat. In panel B an earlier stimulus at an H₁ V interval of 415 msec fails to conduct retrogradely to the bundle of His resulting in an interpolated ventricular beat. The next sinus beat is slightly premature due to the ventriculophasic effect of the interpolated beat. The A H interval of the sinus beat shows no effects of retrograde concealed conduction.

The results of the findings presented

Table I *Electrophysiological data**

Patient (age)	Cycle length	ECG	A H†	H V	AVCS	
					FRP	ERP
1 I M (55)	BCL = 1 150	LAF -60 QRS = 0 12 sec	100	45	345	380
	BCL = 600	"	135	45	400	310
	BCL = 500	"	140	45	345	270
2 P H (64)	SCL = 860-1 180	RBBB + LAF -60	110	45	530	465
	BCL = 850	"	120	45	510	475
3 A M (59)	SCL = 880 920	LAF -60 QRS = 0 12 sec	100	55	555	495
4 J L (66)	SCL = 1 150 1 290	Normal	90	40	345	410
	BCL = 820	"	100	40	460	360
5 D T (60)	BCL = 700	LAF -30	85	45	380	270
6 I E (45)	BCL = 800	Normal	90	50	410	360
7 T M (46)	BCL = 800	LBBB normal axis	125	90	770	770

*All values expressed in milliseconds.

†Abbreviations used

A H = Interval between the atrial electrogram and bundle of His electrogram as recorded by the His bundle catheter

H V = Interval between the His deflection and the earliest evidence of ventricular activity (whether in the His bundle electrogram or the peripheral ECG)

AVCS = (The entire) atrioventricular conduction system

AVN = Atrioventricular node

VSCS = Ventricular specialized conduction system

LRP = Effective refractory period

FRP = Functional refractory period

H₁ V = The shortest interval following depolarization of the bundle of His (during SCL or BCL) at which the ventricle can be effectively stimulated

patients) or outflow tract (two patients). The latter was deliberately utilized as a pacing site because of the near complete absence of Purkinje network in the outflow tract. That the level of block was not at the ventricular muscle level but proximal to this region is indicated by the fact that in each case, regardless of pacing site, ventricular depolarization could be elicited earlier in diastole than the point at which H₂ was blocked. Reference to Table I shows that in every instance the H₁ V interval was shorter by a range of 30 to 220 msec than the H₁ H₂ interval at which H₂ blocked.

Fig 1 (Patient 6) is a representative example. In panels A to C, the right atrium is being paced at a constant cycle length. In panel A, the prematurely evoked His bundle depolarization (H₂) conducts to the ventricle at an H₁ H interval of 410 msec. In panel B, a slightly more premature atrial impulse evokes an earlier His bundle de-

polarization which fails to conduct to the ventricle at an H₁ H₂ interval of 400 msec. In panel C the sequence is identical to that of panel B with the added event that the ventricle is being simultaneously stimulated at an H₁ V_s interval of 380 msec. These findings indicate that the AMR was located somewhere between the bundle of His and the most distal portion of the Purkinje network.

Additional observations were made in two patients (Patients 2 and 3) in whom a retrograde His deflection could be seen during ventricular stimulation. In Fig 2 (Patient 3) panel A, the shortest H₁ H₂ interval (530 msec) which still permitted antegrade conduction to the ventricle is shown. In panel B antegrade conduction fails at an H₁ H interval of 515 msec. In panel C the same preceding cycle length is present as in panels A and B. The ventricle is prematurely stimulated at an H₁ V_s interval of 430 msec, resulting in

Atrial node		VSCS ERP	$H_1 V$	Δ	Ventricular pacing site	Ventricle refractory ($H_1 V$)	Atrium refractory ($I S$)
FRP	TRP						
400	300	(520)	400	40	Apex	410	360
360	310	500	380	—	—	—	300
330	270	315	380	—	—	—	210
495	400	540	395	145	Outflow	345	190
480	400	480	395	85	Outflow	345	115
450	310	530	415	115	Outflow	—	290
450	410	460	440	30	Apex	—	390
440	360	410	380	—	—	—	340
330	200	365	335	30	Apex	130	240
335	315	410	335	75	Apex	325	290
610	450	680	460	220	Apex	400	220

1. Difference between ERP of the VSCS and the $H_1 V$ interval.
 2. A measure of atrial refractoriness. T_1 to T_2 interval from a preceding atrial impulse at which the stimulus (S) is to depolarize the atrium.
 3. Sinus cycle length (paced).
 4. Basic cycle length (paced).
 5. Left bundle branch block.
 6. Right bundle branch block.
 7. Left bundle branch block.
 8. Induced by atrial electrical pacing. No impulse blocked below threshold of $H_1 A$.

retrograde activation of the bundle of His and atria. This indicates that the area(s) of the VSCS which was maximally refractory and thereby prevented antegrade conduction to the ventricles (panel B $H_1 H_2$ interval = 517 msec) was less refractory at the time the retrograde ventricular impulse activated this region and consequently could permit retrograde conduction to the bundle of His (panel C $H_1 H_2$ = 375 msec). This can be explained by the fact that when the ventricles are pre-excited ventricular activation initially begins by muscle-to-muscle depolarization. A few milliseconds later (undetermined) the impulse enters the VSCS. This slight delay causes the retrograde impulse to reach the AVN at a time later in the cardiac cycle when it is less refractory. This explanation is supported by the fact that the interval from the onset of ventricular depolarization (V_1) to the retrograde His deflection (H_1) measures 155 msec which exceeds by 85

msec the longest H-V interval which was obtained (panel A $H_1 V_1$ = 70 msec) just prior to failure of antegrade conduction to the ventricle (panel B).

Fig 3 taken from the same patient demonstrates a phenomenon which might be interpreted as an AMR or gate during retrograde conduction. In panel A a premature ventricular response (V_1) is elicited at an $H_1 V$ interval of 420 msec resulting in delayed retrograde activation of the bundle of His and atria. There is a fully compensatory pause following the induced ventricular beat. In panel B an earlier stimulus at an $H_1 V_1$ interval of 415 msec fails to conduct retrogradely to the bundle of His resulting in an interpolated ventricular beat. The next sinus beat is slightly premature due to the ventriculophasic effect of the interpolated beat. The A-H interval of the sinus beat shows no effects of retrograde concealed conduction.

The results of the findings presented

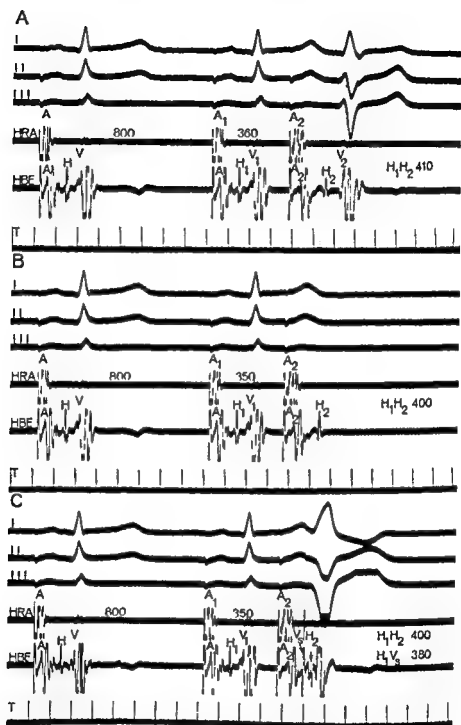


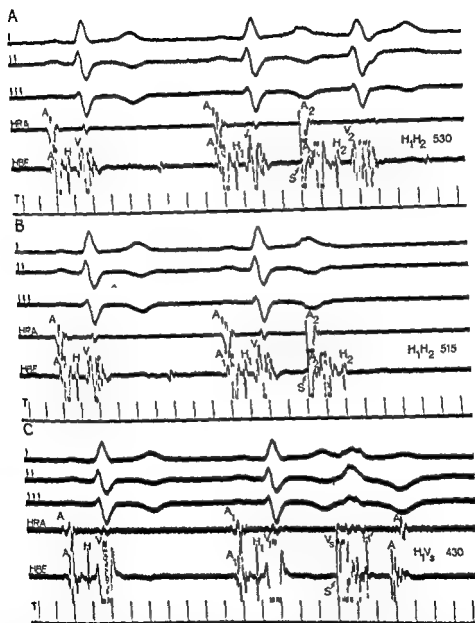
Fig 1 Localization of the site of block of a premature impulse (Patient 6)

In panels A to C records of standard ECG Lead I to III, high right atrial electrogram (HRA), His bundle electrogram (HBE) and time lines (T) at intervals of 10 and 100 msec are shown. A, atrial electrogram; H, His bundle electrogram; V, ventricular electrogram; S, stimulus artifact. In panels A to C the atria are being paced at a constant cycle length of 800 msec with an A-H interval of 85 msec and an H-V interval of 45 msec.

Panel A: A premature atrial depolarization (A) is introduced 360 msec after the preceding atrial impulse (A₁) and is conducted with an A₂-H₂ interval of 135 msec and an H₂-V₂ interval of 10 msec associated with a pattern of right bundle branch block (RBBB) and left anterior fascicular block (LAF). The H₁-H₂ is 410 msec.

Panel B: A₂ is slightly more premature, occurring at an A₂ interval of 350 msec and is conducted with an A₂-H₂ interval of 135 msec. H₂ fails to conduct anterogradely at an H₁-H₂ interval of 400 msec.

Panel C: The sequence is identical to that of Panel B. In addition, the ventricle (V) is simultaneously being stimulated at an H₁-V₁ interval of 380 msec. Note the integrated His is still seen at an H₁-H₂ interval of 400 msec.



F Localization of the site of block of a premature impulse (Patient 3). Sinus rhythm; initially presented with LAF (-30°) in each panel at a cycle length of 900 msec, with a V-H interval of 110 msec and an H-V interval of 50 msec.

Panel A: A premature atrial impulse (A) introduced 480 msec after the preceding sinus impulse (A₁), conducted with an A-H interval of 150 msec. The resulting prematurely evoked His bundle depolarization (H₁) occurs at an H₁-H₁ interval of 530 msec and is conducted with an H₁-V interval of 40 msec, as occurred with a pattern of RBBB.

Panel B: A more premature (A) (A = 40 msec) and conducted with a delay of 150 msec, to the bundle of His (H₁). The H₁-H₁ interval is 515 msec, with block occurring distal to the bundle of His.

Panel C: The atrial prematurely stimulated at a H-V interval of 430 msec, resulting in retrograde depolarization of the bundle of His (H₁) as well as the atrium. The A-H interval is 150 msec, and the H₁-H₁ interval is 575 msec.

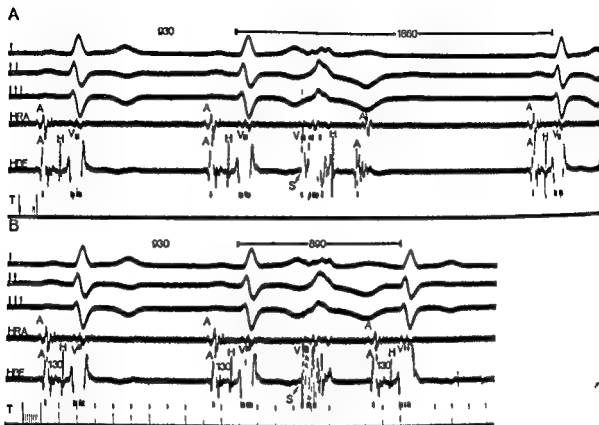


Fig. 3 Retrograde conduction delay and block below the bundle of His (Patient 3). In panels A and B sinus rhythm is present at a cycle length of 900 msec. See text for discussion.

Fig. 4 Delay of a premature impulse in the proximal VSCS allowing distal recovery (Patient 1). To the right of each panel is a simultaneous recording of ECG Leads I, II, V₁, and V₆. Pacing stimuli are being delivered through a catheter lying in the coronary sinus and are associated with inverted P waves in Leads II and III. The sequence of atrial depolarization is reversed with the low atrial septum recorded in the HBE preceding the HRA.

In Panels A to D, the atria are being paced at a constant cycle length of 1150 msec, and atrial premature depolarizations (APDs) are introduced progressively earlier in the basic atrial cycle. Left anterior fascicular block is present with an axis of -60° with a QRS duration of 0.12 sec. The A-H interval is 100 msec, and the H-V interval is 45 msec.

Panel A: APD introduced 490 msec after the last paced atrial beat is conducted with an A₁-H₂ interval of 130 msec. The resulting H₁-H₂ interval is 520 msec; the premature His depolarization thus evoked is conducted to the ventricle with an H₁-V₂ interval of 70 msec, associated with a pattern of RBBB and LAF.

Panel B: APD introduced at an A₁-A₂ interval of 470 msec conducts to the bundle of His with an A₂-H₂ interval of 140 msec. Block of H₂ occurs at an H₁-H₂ interval of 510 msec.

Panel C: APD introduced at an A₁-A₂ interval of 440 msec conducts with an A₂-H₂ interval of 140 msec. H₂ now occurs at an H₁-H₂ interval of 480 msec and, although more premature than its counterpart in Panel B, is conducted to the ventricle with an H₂-V₂ interval of 210 msec, associated with a pattern of left bundle branch block (LBBB). Note that primary I wave changes are present with the LBBB beat, reflecting the repolarization abnormality obvious in the control beats.

Panel D: APD introduced at an A₁-A₂ interval of 430 msec is conducted to the bundle of His with an A₂-H₂ interval of 145 msec, resulting again in block below the His at an H₁-H₂ interval of 460 msec.

Two HBE were recorded in this instance, utilizing different combinations of bipolar leads from the tripolar catheter. The failure of the blocked H₂ to appear in the lower HBE (Panel D) emphasizes how catheter position may lead to the erroneous diagnosis of block within the A-V node.

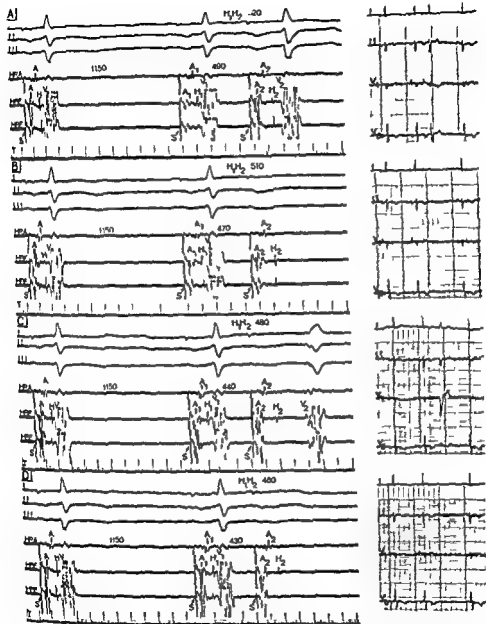


Fig 4 For legend see opposite page.

in Figs 2 and 3 suggest that muscle delay by affording the VSCS recovery time may allow a ventricular response elicited during the ERP of VSCS to propagate retrogradely. Additional delay in some area of the VSCS must also be postulated for two reasons (1) No change in configuration or duration of the ventricular beat was observed during progressively more premature stimulation of the ventri-

cle. Such changes might have suggested more muscle to muscle propagation as increasing conduction delay was encountered (2) No latency or multiple firing was seen despite significant delays.

Fig 4 is an example of differential refractoriness in the VSCS in man (Patient 1). In panel A H_2 arrives in the refractory period of the right bundle branch at an H_1H_2 interval of 520 msec. In panel B an

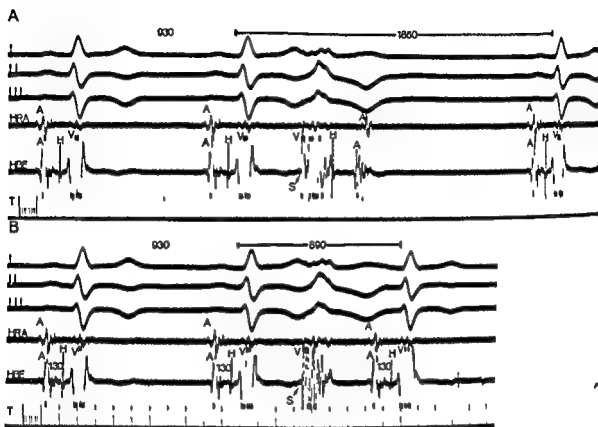


Fig 3 Retrograde conduction delay and block below the bundle of His (Patient 3). In panels A and B sinus rhythm is present at a cycle length of 930 msec. See text for discussion.

Fig 4 Delay of a premature impulse in the proximal VSCS allowing distal recovery (Patient 1). To the right of each panel is a simultaneous recording of LCG Leads I, II, V₁ and V₆. Pacing stimuli are being delivered through a catheter lying in the coronary sinus and are associated with inverted T waves in Leads II and III. The sequence of atrial depolarization is reversed with the low atrial septum recorded in the HBE preceding the HRA.

In Panels A to D the atria are being paced at a constant cycle length of 1150 msec and atrial premature depolarizations (APDs) are introduced progressively earlier in the basic atrial cycle. Left anterior fascicular block is present with an axis of -60° with a QRS duration of 0.12 sec. The A-H interval is 100 msec, and the H-V interval is 45 msec.

Panel A APD introduced 490 msec after the last paced atrial beat is conducted with an A-H interval of 130 msec. The resulting H₁-H₂ interval is 520 msec; the premature His depolarization thus evoked is conducted to the ventricle with an H₂-V₂ interval of 70 msec associated with a pattern of RBBB and LAF.

Panel B APD introduced at an A₁-A₂ interval of 410 msec conducts to the bundle of His with an A-H interval of 140 msec. Block of H₂ occurs at an H₁-H₂ interval of 510 msec.

Panel C APD introduced at an A₁-A₂ interval of 440 msec conducts with an A-H interval of 140 msec. H₂ now occurs at an H₁-H₂ interval of 480 msec and although more premature than its counterpart in Panel B is conducted to the ventricle with an H₂-V₂ interval of 210 msec associated with a pattern of left bundle branch block (LBBB). Note that primary T wave changes are present with the LBBB beat reflecting the repolarization abnormality obvious in the control beats.

Panel D APD introduced at an A₁-A₂ interval of 430 msec is conducted to the bundle of His with an A-H interval of 145 msec resulting again in block below the His at an H₁-H₂ interval of 460 msec.

Two HBE were recorded in this instance utilizing different combinations of bipolar leads from the tripolar catheter. The failure of the blocked H₂ to appear in the lower HBE (Panel D) emphasizes how catheter position may lead to the erroneous diagnosis of block within the A-V node.

of LKPs (370 and 470 msec) of the VSCS in this patient. The limitation of the usual manner of defining the ERP is readily apparent in a patient such as this.

Fig. 3 demonstrates an interesting phenomenon observed in one patient (Patient 3). Appropriately timed spontaneous premature junctional extrasystoles were confined within the conduction system proximal to the AVR. In panel A a prematurely evoked His depolarization occurs at an $H_1 H_2$ interval of 320 msec which is less than the ERP of the VSCS for this patient (see Table I) and thus fails to conduct to the ventricle. In panel B following the same preceding cycle length a spontaneous His extrasystole occurs at an $H_1 H_2$ interval of 300 msec and also fails to propagate to the ventricle. However it does propagate retrogradely and thus simulates electrocardiographically a blocked premature atrial beat as evidenced by the inverted P waves in Leads II and III. Junctional beats occurring outside the ERP of the VSCS (i.e. at an $H_1 H_2$ interval greater than 530 msec) conducted successfully to the ventricle. In three patients (1, 2 and 4) the ERP of the VSCS was shortened by decreasing the basic cycle length of atrial pacing. In two patients (1 and 4) the ERP of the VSCS was sufficiently shortened so that block below the His during premature atrial stimulation could not be elicited. Atrial refractoriness was observed to decrease in all patients at higher paced rates.

Discussion

Block of premature impulses distal to the bundle of His has been described in animal studies^{2, 3, 11, 14} and in man.^{15, 16} In addition block of retrograde propagation of ventricular depolarization has been shown to occur at various levels of the VSCS.^{4, 17, 18}

In the present study an AVR was demonstrated in the human heart which limited the propagation of premature impulses arising on either side of it. When block of premature supraventricular impulses occurred distal to the bundle of His in our selected patients the ventricular muscle was invariably excitable at an earlier point in diastole than that at which antegrade conduction failed. This confirms in man that muscle refractoriness is not the cause of such block. Block of

retrograde conduction below the AVR (Fig. 3) provides a mechanism in man for the failure of some interpolated premature ventricular beats to show the effects of concealed conduction in the A-V node. This may also provide protective mechanism against premature ventricular beats initiating arrhythmias on the basis of macroreentry utilizing the proximal portions of the VSCS.

In vitro studies have indicated that during antegrade conduction premature impulses with a coupling interval shorter than the refractory period of the AVR can be successfully conducted when sufficient delay in a more proximal region of the VSCS allows the more distal AVR to recover.⁴ Our findings of a similar phenomenon (Fig. 4) in man are in agreement.¹⁹ Thus a gap in conduction may occur because of delay in the VSCS analogous to the A-V nodal delay responsible for the A-V nodal gap phenomenon. There is an essential difference however between these two mechanisms. The $H_1 H_2$ interval at which conduction resumes in the A-V nodal gap is longer than that at which block below H_2 occurs while in the VSCS gap the $H_1 H_2$ interval is shorter than that at which block below H_2 occurs. In the former A-V nodal delay allows the AVR to recover in the latter delay in some area of the VSCS proximal to the AVR allows it to recover. Since conduction resumes at closer coupling intervals the phenomenon of delay in the VSCS allowing recovery represents another type of so called 'supernormal' conduction.

The approach of the present study may be useful in future studies on the effects of pharmacological agents which depress conduction in the VSCS because it emphasizes the need for independent assessment of the refractoriness of muscle and specialized conducting tissues.

Summary

The area of maximum refractoriness (AVR) or gate in the ventricular specialized conduction system (VSCS) has not been previously demonstrated in the human A-V conduction system. Animal studies have shown an AVR proximal to the Purkinje muscle junction.

Seven patients were studied using His

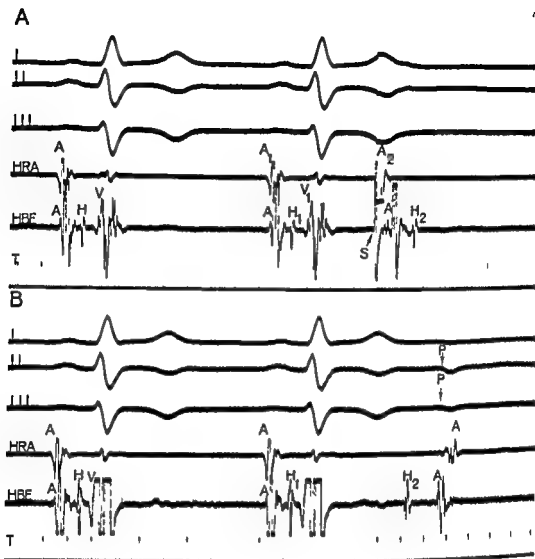


FIG. 5. Concealed junctional extrasystole simulating a blocked premature atrial impulse (Patient 3).

Panel A. Sinus rhythm is present with a cycle length of 880 msec. The A-H interval is 100 msec, and the H-V interval is 55 msec. Note the normal sequence of atrial depolarization proceeds from the HRA to the low atrial septal deflection recorded in the HBL. An APD introduced at an A₁A₂ interval of 480 msec is blocked below the bundle of His with an H₁H₂ interval of 520 msec.

Panel B. Following the same preceding cycle length, a spontaneous His extrasystole (H₂) occurs at a slightly shorter H₁H₂ interval of 500 msec and fails to conduct integrally. It is however retrogradely conducted to the atria with an H-A interval of 150 msec and is associated with an inverted P wave in Leads II and III. The polarity of the His deflection as well as the sequence of atrial depolarization is reversed.

earlier His bundle response at an H₁H₂ interval of 510 msec fails to propagate to the ventricle. In panel C, H₂ arrives at an H₁H₂ interval of 480 msec and is conducted with a very long H-V interval of 210 msec. Ventricular depolarization yields a pattern of left bundle branch block (LBBB), suggesting that delay occurred proximal to the AMR in the right-sided VSCS, allowing recovery of the latter with resultant propagation to the ventricle. In panel D, H₂ is even more premature, at an H₁H₂ interval of 460 msec, and once

again fails to conduct to the ventricle. Refractory periods were carefully repeated in this patient decreasing the prematurity of the test stimulus by 2 msec intervals. On each determination (a) all H₁H₂ intervals \geq 520 msec conducted to the ventricle; (b) H₁H₂ intervals between 500 and 510 msec resulted in block below H; (c) conduction resumed between intervals of 500 and 470 msec with LBBB and a long H₁V₂ interval; and (d) H₁H₂ intervals less than 470 msec also resulted in block below H₂. For this reason, Table I indicates

A new roentgenographic assessment of anatomic deformity in calcific aortic stenosis

Paul D. Stein, M.D.
Oklahoma City, Okla.

The aortic valve can be visualized as if looking directly into the orifice by obtaining roentgenograms with the x-ray beam directed through the heart on a line from the right axilla to the left iliac crest.¹ Even though there is variation of the actual orientation of the aortic valve leaflets in patients with aortic ball valve prostheses (in whom the area of the orifice is precisely known) showed that the orifice can be measured by this method with 90 percent accuracy in 80 per cent of patients.¹ Aortograms taken at this projection have been utilized effectively to measure the functional cross sectional area of the aortic valvular orifice in normal subjects as well as in patients with diseased aortic valves.^{1,2} The injection of contrast material is necessary to evaluate the orifice if the valve is not calcified. In the presence of valvular calcification plain roentgenograms by the use of this projection can show the calcified outline of the orifice. By noninvasive roentgenographic techniques therefore the pathologic deformity of the stenotic calcific aortic valve can be defined with close approximation to the actual specimen. In this communication the technique is illustrated and patients are described in

whom the method appeared to be of practical value.

Methods

Plain films of the chest are obtained with the patient supine and the x-ray beam directed through the heart at a 45 degree superior elevation in the frontal plane and a 0 degree elevation in the sagittal plane.¹ At this angle the aortic valve can be visualized as if looking directly into the orifice. Any dimension of the orifice that is outlined by calcium can be measured from the roentgenogram. In order to compensate for magnification the position under the chest of the calcified valve is located by fluoroscopy. Localization of the valve in this way permits one to measure the distance from the x-ray tube to the valve (target to-object distance). Dimensions measured on the roentgenogram are assessed after proper compensation for magnification by the following equation:

$$\text{Apparent length} = \frac{\text{Actual length} \times \text{Target to-object distance}}{\text{Target to film distance}}$$

An approximate exposure time of 1/12 sec at 400 Ma and 100 kv has been adequate.

From the Department of Medicine, University of Oklahoma School of Medicine and Veterans Administration Hospital, Oklahoma City, Okla.
Supported in part by the Veterans Administration Research Service and Oklahoma Heart Association.
Received for publication June 18, 1971.
Reprint requests: Paul D. Stein, M.D., Veterans Administration Hospital, 921 N. E. 13th St., Oklahoma City, Okla. 73104.

bundle electrograms Single atrial premature depolarizations (APD) were introduced progressively earlier during the basic atrial cycle, until a point was reached where the APD no longer conducted to the ventricles The region of block in these seven selected patients was distal to the bundle of His Single ventricular depolarizations were then likewise introduced prematurely throughout mid late diastole In all seven patients the ventricle could be depolarized earlier in the basic cycle (30 to 220 msec) than the point at which block below the His occurred, localizing the AMR between the bundle of His and the ventricular muscle A similar AMR was found during retrograde conduction

A mechanism analogous to the A V nodal "gap" phenomenon exists in the VSCS Thus, late premature atrial impulses may fail to conduct distal to the bundle of His while earlier beats encounter delay in an area of the VSCS proximal to the AMR allowing propagation to the ventricle This represents another mechanism of so called supernormal conduction

The present study emphasizes simultaneous evaluation of the refractory state of specialized cardiac conducting tissue and muscle Such an approach may be useful in future studies of drugs which depress subjunctional tissues

REFERENCES

- 1 Cannon DS Goldreyer BN and Damato AN The atrioventricular conduction system in left bundle branch block with normal QRS axis Circulation (In press)
- 2 Hoffman BF Cranefield PI and Stuckey JH Concealed conduction Circ Res 9:194 1961
- 3 Hoffman BF Moore LN Stuckey JH and Cranefield PI Functional properties of the atrioventricular conduction system Circ Res 13 308 1963
- 4 Mendez C Mueller W J Merideth J and Moe G K Interaction of transmembrane potentials in canine Purkinje fibers and at Purkinje fiber muscle junctions Circ Res 24 361 1969
- 5 Moore LN Preston J B and Moe G K Durations of transmembrane action potentials and functional refractory periods of canine false tendons and ventricular myocardium Comparisons in single fibers Circ Res 1:259 1965
- 6 Hoffman BF Kao CY and Stuckey EE Refractoriness in cardiac muscle Am J Physiol 190 4:3 1957
- 7 Myerburg RJ Stewart J W and Hoffman II J Electrophysiological properties of the canine peripheral A V conduction system Circ Res 26 361 1970
- 8 Myerburg RJ Gelbrund H and Hoffman BF Functional characteristics of the gating mechanism in the canine A V conducting system Circ Res 28 136 1971
- 9 Scherling II J Lau S H Helfant R H Berkowitz W D Stein E and Damato A N Catheter technique for recording His bundle activity in man Circulation 39 13 1969
- 10 Kraybill O Mandok J J and Mendez C Studies on veratrum alkaloids XVI The action of epinephrine and of veratramine on the functional refractory period of the atrioculventricular transmission in the heart lung preparation of the dog J Pharmacol Exp Ther 103 412 1951
- 11 Moe G K Preston J B and Burlington H Physiological evidence for a dual A V transmission system Circ Res 14 337 1956
- 12 Wit A L Weiss M B Berkowitz W D Rosen K M and Steiner C Patterns of atrioventricular conduction in the human heart Circ Res 27 345 1970
- 13 Moe G K Mendez C and Han J Aberrant A V impulse propagation in the dog heart A study of functional bundle branch block Circ Res 16 261 1965
- 14 Mendez C Han J and Moe G K Comparison of the effects of epinephrine and vagal stimulation upon the refractory periods of the A V node and the bundle of His Arch Exp Path Pharmacol 248 99 1964
- 15 Damato A N Lau S H Patton R D Steiner C and Berkowitz W D Study of atrioventricular conduction in man using premature atrial stimulation and His bundle recordings Circulation 40 61 1969
- 16 Wit A L Damato A N Weiss M B and Steiner C Phenomenon of the gap in atrioventricular conduction in the human heart Circ Res 27 679 1970
- 17 Moore LN Microelectrode studies on retrograde concealment of multiple premature ventricular responses Circ Res 20 88 1967
- 18 Castillo C and Castellanos A Retrograde activation of the His bundle in the human heart Am J Cardiol 27:264 1971
- 19 Gallagher J J Damato A N Varghese P J Crick A R Josephson M I and Lau S H Gap in A V conduction Type I and Type II Clin Res 20 (Abstr) 373 1972

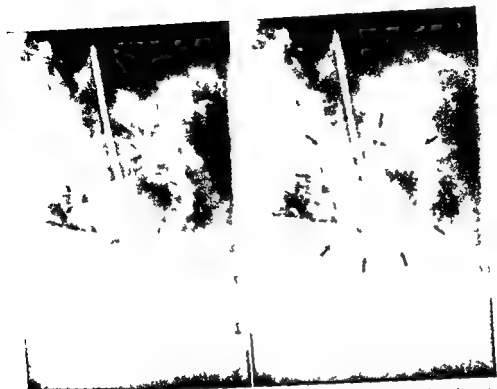


Fig 3 Roentgenogram of the same patient taken at a projection specifically designed to show the aortic valve as if looked directly into the orifice. The calcified annulus appears circular indicating negligible distortion of the projected image. The orifice shown within the calcified valve appears as an eccentric elongated radiolucent zone. A 1.2 mm. diameter picemaker catheter is positioned in the right ventricle and is superimposed over the orifice. Dimensions of the orifice can be judged by comparison with the diameter of the catheter. For clarity, the orifice is outlined by dots in the duplicate illustration at right. The annulus is shown by arrows.

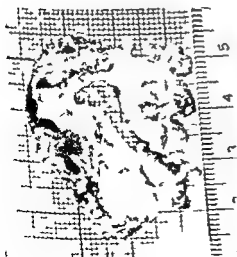


Fig 3 Excised aortic valve (same patient as in Figs. 1 and 2). Lines on the grid in the background are spaced at 1 mm. intervals.



Fig 4 Roentgenogram of excised aortic valve (same valve as in Fig 3). Radiopaque dots are placed at 1 cm. intervals. The central radiolucent zone is the orifice. A nearly radiolucent (gray) rim of tissue is shown between the lumen and calcified region.



Fig 1 Posterior anterior chest film of a patient showing heavy deposits of calcium in the region of the aortic valve (arrows)

quate in most patients. A grid cassette with high speed Radelin* screens and GAF[†] film† is routinely utilized.

The aortic valve illustrated in this study was re-evaluated after it was surgically excised at the time of insertion of a ball valve prosthesis. The leaflets were reconstructed immediately after they were removed in the operating room. Photographs and roentgenograms of the excised valve were obtained. The configuration and dimensions of the valve were evaluated from these films.

Results

Heavy deposits of calcium in the region of the aortic valve of a man with clinical evidence of severe aortic valvular disease were shown on chest films (Fig 1). At cardiac catheterization a 58 mm Hg peak pressure gradient was measured across the aortic valve. Moderate aortic regurgitation was shown on cine aortograms.

A plain roentgenogram of the calcified valve was taken with the patient supine and the x-ray tube elevated 45 degrees in the frontal plane. The configuration of the orifice, outlined by calcium is shown (Fig 2).

At surgery a heavily calcified valve

was removed. The configuration of the orifice was similar to that shown on the 45 degree angle roentgenogram (Fig 3). Roentgenograms of the excised valve also showed a similar configuration (Fig 4). The central radiolucent area of this roentgenogram represents the actual lumen as shown on the photograph of the valve. Between the lumen and heavy calcific deposits there is a less radiolucent fibrotic rim (Fig 4). This rim is completely radiolucent and, therefore, inapparent on the roentgenogram of the valve taken prior to surgery (Fig 2). The dimensions measured from this oblique chest film correspond to the dimensions outlined by calcific deposits. The length of the orifice appeared to be 2.8 cm on the preoperative film of the orifice (Fig 2) and 2.5 cm on the roentgenogram of the excised valve (Fig 4). Similarly, a sample width of the valve appeared to be 0.7 cm on the special chest film and 0.6 cm on the postexcisional film. Since a noncalcified inner rim of fibrous tissue was present, the actual dimensions of the orifice (length, 1.6 cm; width, 0.5 cm) were somewhat smaller (Fig 3).

Discussion

This method is particularly advantageous because it is noninvasive and the results directly reflect the morphology of the abnormal aortic valve. In patients with heavily calcified valves, the technique permits a preoperative assessment of the anatomy of the deformed valve that closely corresponds to the configuration and dimensions of the actual specimen.

Evaluation of the results requires recognition of the fact that the cross-sectional area of the actual orifice will be smaller than the area outlined by calcium. In some patients, however, the area enclosed by calcium will be small enough to indicate critical stenosis, irrespective of the presence of a central noncalcified radiolucent area. This was demonstrated in three patients: whom the area circumscribed by calcium was 0.6, 0.7 and 0.8 sq cm, respectively, and in whom nearly identical orifice areas were measured at surgery. Consequently, the method in some patients can be utilized to determine if a valvular deformity is severe enough to warrant a surgical intervention. In appropriate patients, the

*U S Radium Corp. Morris town N J
†GAF Corp. New York N Y

Ejection fraction in anomalous origin of the left coronary artery from the pulmonary artery

James A Menke*

Reda M Shaher MD

Grace S Wolff MD

Albany NY

The indications for surgery in the case of anomalous left coronary artery from the pulmonary artery are not readily agreed upon. Nadas and associates¹ suggested that if there is a left to right shunt at pulmonary arterial level demonstrated by selective arteriography ligation of the anomalous vessel should be carried out. Nora and colleagues² suggested that the child with anomalous left coronary artery arising from the pulmonary artery be managed medically until the age of 5 years when definitive surgical therapy could be undertaken. Perry and Scott³ divided infants and children with this anomaly into three groups depending on the degree of collateral circulation and assigned to each group a different type of management. Prompted by these differences of opinion and the fact that we have had 5 cases surgically treated by ligation of the anomalous left coronary artery we decided to look for other parameters that would help selection of patients with this anomaly for ligation of the vessel. We have chosen the ejection fraction because it is a quantitative measurement which has good correlation with myocardial function.⁴

Materials and methods

Between 1966 and 1971 5 cases of anomalous left coronary artery from the pulmonary artery were seen at Albany Medical Center Hospital. In addition 5 cases were found in the literature on whom ejection fraction or ventricular volumes were reported.⁴⁻⁸ Eight of these 10 patients were treated surgically: 6 by ligation of the anomalous coronary artery, one by suture of orifice through an arteriotomy and one by anastomosis of anomalous vessel to the aorta. Two patients were treated medically. Of the 8 that had surgery there were 3 girls and 5 boys. The ages ranged from 5 weeks to 12 years. Three of these patients survived surgery. Of the 2 medically treated the one alive was 9 years old when diagnosed, the other died at the age of 3½ months. All were investigated by angiocardiography but pressure and oxygen saturation data were available to us for only 6 patients. Of the 6 that died autopsy information was available to us in 4 cases.

In 8 patients the ejection fractions were calculated from preoperative angiocardiograms. In the remaining 2 they were calculated from postoperative angiocardiograms.

From the Division of Pediatric Cardiology, Albany Medical College, Albany, NY.

Received for publication May 22, 1971.

Reprint requests to: Reda M. Shaher, MD, Head, Division of Pediatric Cardiology, Albany Medical Center Hospital, Albany, NY 12208.

*Assistant, Albany Medical College, Albany, NY.

method could therefore eliminate the necessity of cardiac catheterization

Summary

By utilization of noninvasive roentgenographic methods one can define the anatomic deformity of calcified aortic valves with close approximation to the actual specimen. This is accomplished by visualization of the area circumscribed by calcium on plain films obtained at a projection specifically suited for this purpose. Films are obtained as if looking directly into the orifice by directing the x ray beam through the heart on a line from the right axilla to the left iliac crest (45 degree superior elevation in the frontal plane). The dimensions

outlined by calcium can be reliably measured. Consequently, the dimensions of the orifice can be closely approximated. In occasional patients with heavily calcified, severely stenotic aortic valves the technique may obviate the necessity of cardiac catheterization.

The author would like to thank Dr James W Hartsuck for his skillful surgical dissection of the aortic valve illustrated in this study.

REFERENCES

- 1 Stein P D Roentgenographic method for measurement of the cross sectional area of the aortic valve. *Am Heart J* 81:667 1971
- 2 Stein P D and Munter W New functional concept of valvular mechanics in normal and diseased aortic valves. *Circulation* 64:101 1971

Pressures						Time
RA	RI	PA	LA	LV	ao	
93	76/6	26/12	16/10 wedge	95/0 1 0/3	95/60 120/30	Preop Postop
0	50/5	20/10 VI = 15		110/15	110/60 VI = 80	Preop
8/2 VI = 6	40/4	40/25 VI = 32		90/10	90/60	Preop
	40/5	37/10 VI = 22		90/20	80/50 VI = 62	Preop
2	30/6	30/15 VI = 20			50/40	1 reop
2	8/10	33/20 VI = 26		80/35	80/60 VI = 40	Preop
6 V = 1 M = 1	46/6 E D	40/14 VI = 20	1 = 15 1 = 8 VI = 6		112/86 VI = 90 F 1	Preop
4 1 = 3 VI = 5	31/4 E D	36/21 M = 24		75/12 19 E D		Postop

heart op. = opera PA = pulmonary artery RA = right atrium RI = right ventricle SVC = superior vena cava

a step up in oxygen saturation who survive regardless of therapy employed Group 2 those patients who have a left to right shunt at the pulmonary arterial level demonstrated angiographically which is not large enough to be detected by oxygen saturation (in this group there is no definite difference between those treated surgically and those treated medically surgery should be undertaken when the patient reaches 1 years of age) Group 3 those patients with no left to right shunt The only therapy is anastomosis of the anomalous left coronary artery to the aorta

Of the 44 cases with hemodynamic and angiographic studies mostly collected from the literature by Perry and Scott,¹⁸ 18 were in Group 1 22 in Group 2 and 4 in Group 3 Since the mean age of Group 1 was 61 years it would seem that most patients seen during the first year of life will fall into Groups 2 and 3 All 4 patients with preoperative hemodynamics and angiographic data seen at Albany Medical Center Hospital were in Group 2 The authors believe that the ejection fraction would be of a particular help in the selection of Group 2 and 3 patients for

surgery It would seem that those patients with ejection fractions more than 0.55 would be good candidates for surgery The vessel should be anastomosed to the aorta if it is large enough to accomplish the procedure Those with ejection fractions less than 0.35 have a poor prognosis regardless of the method employed and should be treated by vigorous medical therapy Since none of the patients in this study had an ejection fraction between 0.35 and 0.55 the indications for surgery in this group should await further study

The authors believe that in addition to the symptoms clinical findings electrocardiograms and chest x ray the ejection fraction may also be used to follow the progress of these patients and to assess the surgical result Determination of the ejection fraction by ultrasound^{11, 12} could be the method of choice in the follow up of these patients

Summary

The ejection fraction of 10 patients with anomalous origin of the left coronary artery from the pulmonary artery has been studied Five were seen at Albany Medical

Table I Cardiac catheterization data

Patient	Oxygen saturations							
	IVC	SVI	RA	RI	LA	LI	LI	to
1 C C	69	79	80	78	81		96	96
2 (Bookstein ⁴) D V								
3 D I	74	74	77	76	76		91	91
4 C W	67	69	62	64	63		93	91
5 (Graham et al ⁴)								
6 J W	71		67	55	66			
7 M W	49	50	51	49	49		89	91
8 (Bookstein ⁴) D M								
9 (Wagner et al ⁴) D B		36 0	86 9	85 0	83 4	96 5		FA 96
		64 5	63 0	57 8	62 5		99 5	
10 (Bookstein ⁴) J H								

Abbreviations: to = aorta; ED = end diastolic; LA = femoral artery; IVC = inferior vena cava; LA = left atrium; LV = left ventricle.

grams. In our patients (Nos 1, 3, 4, 6, and 7), ejection fractions were calculated according to the method described by Kennedy and associates⁵ from single plane cine angiocardiograms in the anteroposterior projection. Of the 5 cases collected from the literature the ejection fraction for Patients 2, 8, and 10 were calculated from ventricular volumes reported by Bookstein.⁴ The method for determining the ejection fraction in Patient 5 was that of Dodge and Sandler.⁸ In Patient 9 ejection fractions were determined from ventricular volumes measured by the method of Dodge and Sandler.⁸ The patient, D B, was reported in 1967⁹ to be one year and 9 months old and doing well. Later, she developed congestive heart failure and died at the age of 2 years 9 months.¹⁰ The Kennedy group⁵ has shown that ventricular volumes and ejection fractions calculated from biplane cineangiography and from single plane angiography correlate well with each other.⁵

Results

Table I presents the cardiac catheterization results and Table II presents the ejection

fractions of the 10 patients studied in this report.

The 4 patients who survived have ejection fractions between 0.84 and 0.99. The 6 patients who died had ejection fractions between 0.36 and 0.13.

Discussion

Graham and co workers⁴ state that the ejection fraction has good correlation with myocardial function and that if the ejection fraction drops below 0.50 it is indicative of myocardial dysfunction. Our studies support this conclusion for those patients with an ejection fraction above 0.50 did well and those below 0.36 died. Our results indicate the possibility of determining a scale of ejection fractions,² and that some where between 0.35 and 0.55 is the point above which surgery can be undertaken with reasonable safety and below which the prognosis is poor with or without surgery.

Perry and Scott² classified the infant and children with anomalous left coronary artery arising from the pulmonary artery into three groups: Group 1 those patients with a left to right shunt at the pulmonary arterial level demonstrated by

- 6 Bookstein J J Aberrant left coronary artery
Am J Roentgenol 91:1515 1964
- 7 Dodge H T Sandler H Ballen P W and
Lord J D Jr Use of biplane angiocardio-
graphy for measurement of left ventricular volume
in man Am HEART J 162 1960
- 8 Dodge H T Sandler H Baxley W A
and Hawley R R Usefulness and limitation
of radiographic methods for determining left
ventricular volume Am J Cardiol 18 10 1966
- 9 Wagner H R Nadas A S and Hugenholz
P G Anomalous left coronary artery originat-
ing from the pulmonary artery Pediatrics
40:370 1967
- 10 Ellison Curtis Boston Children's Hospital
Boston Mass personal communication
- 11 Lombo J F Russell R O Rackley C E
and Foster G L Comparison of stroke volume
and cardiac output determination by ultra-
sound and dye dilution in acute myocardial
infarction Am J Cardiol 27 630 1971
- 12 Fortuin N J Hood W P Sherman M F
and Craige E Determination of left ven-
tricular volumes by ultrasound Circulation
44 575 1971

Table II Ejection fractions in anomalous left coronary artery from the pulmonary artery

Patient	Cath pre or postop	Ejection fractions	Existence of shunt	Surgery	Prognosis
1 C C	Preop		Angio-RCA to col lateral to ALCA to PA		
	Postop	0.84		Yes ligation at 6 mo	Alive at 9 yr
2 (Bookstein ⁶) D V	Preop	Approx 0.72	Angio-RCA to col lateral to ALCA to PA	No	Alive at 9 yr
3 D T	Preop	0.67	Angio-RCA to col lateral to ALCA to PA	Yes at 12 yr suture of orifice	Alive at 15 yr
4 C W	Preop	0.55	Angio-RCA to col lateral to ALCA to PA	Yes ligation at 6 mo	Alive at 27 mo.
5 (Graham et al ⁴)	Preop	0.36	Angio-RCA to col lateral to ALCA to PA	Yes ligation at 6 wk	Died second po top day at 6 wk
6 J W	Preop	0.31	Angio-RCA to col lateral to ALCA to PA	Yes ligation at approx 9 mo	Died 6 mo postop. in severe CHF at 15 mo. of age
7 M W	Preop	0.23	Angio-RCA to col lateral to ALCA to PA	Yes ligation at 2½ mo	Died po top at 2½ mo. of age
8 (Bookstein ⁶) D M	Preop	0.21	None demonstrated	No surgery just medical management	Died at home at 3 mo. of age
9 (Wagner et al ⁹) D B	Postop	0.184	Small shunt at surgery	Yes ligation at 5 wk	Died at 2 yr 9 mo in severe CHF
10 (Bookstein ⁶) J H	Preop	0.13	Angio-RCA to col lateral to ALCA to PA	Yes anastomosis to aorta at 4 mo. of age	Died a few hours postop at 4 mo. of age

Abbreviations: ALCA = anomalous left coronary artery; Angio = angiography; Approx = approximately; Cath. = catheterization; CHF = congestive heart failure; RCA = right coronary artery.

Center Hospital and 5 were collected from the literature. The 6 patients who died had an ejection fraction less than 0.36. The 4 survivors had an ejection fraction more than 0.55. It has been suggested that this measurement will help in the selection of patients for surgery and the follow up of patients with this anomaly.

REFERENCES

- Nadas A S, Gamboa R and Hugenoltz P G. Anomalous left coronary artery originating from the pulmonary artery. Report of two surgically treated cases with a proposal of hemodynamic and therapeutic classification. *Circulation* 29:167, 1964.
- Nora J J, McNamara D G, Hallman G L, et al. Medical and surgical management of anomalous origin of the left coronary artery from the pulmonary artery. *Pediatrics* 43:405, 1968.
- Perry L W and Scott L P. Anomalous left coronary artery from pulmonary artery. Review of eleven cases: review of indications for and results of surgery. *Circulation* 41:1043, 1970.
- Graham T I Jr, Volberg F M Jr, Cline H F, et al. Severe mitral insufficiency in early infancy associated with anomalous origin of left coronary artery from pulmonary artery. *Am J Cardiol* 23:858, 1969.
- Kennedy S W, Trenholme S E and Jasser J S. Left ventricular volume and mass from single plane cine angiocardiogram. A comparison of anteroposterior and right anterior oblique methods. *Am Heart J* 80:343, 1970.

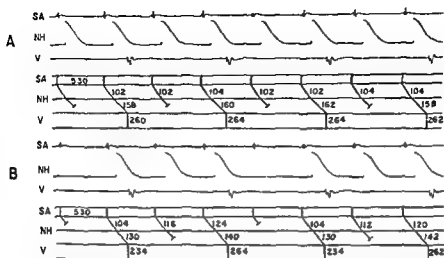


Fig 1 A and B Transmembrane potential from an NH fiber (NH) are shown with surface electrograms recorded from the S-A nodal region (SA) and the ventricles (V). Sinus rhythm with little variation of the cycle length (approximately 530 msec) is present. The ladder diagrams show sequence of A-V conduction with A-V NH-V and total A-V conduction time in milliseconds. Regular 2:1 block with fixed long A-V interval (A) and with alternation of A-V interval (B) are seen. For details see text.

perfusion fluid was saturated with 95 per cent O_2 + 5 per cent CO_2 .

A ventricular electrogram was recorded by two small surface electrodes attached to the right ventricular apex and to the left ventricular base. In some experiments a small bipolar electrode with an interelectrode distance of 1 mm was attached adjacent to the S-A node to record an atrial electrogram. Most preparations were driven at a constant rate by square wave pulses of twice threshold intensity through a bipolar stimulating electrode placed near the S-A node. The rate of stimulation in individual hearts was set 10 to 15 beats per minute higher than the intrinsic sinus rate in the majority of experiments while rapid atrial stimulation at the rate of 300 per minute or higher was used in others to simulate atrial flutter. A-V conduction was studied in some hearts under spontaneous sinus rhythm. Glass microelectrodes were used to record transmembrane potentials from various regions of the A-V junction. The potential were amplified by a neutralized input capacity amplifier and Tektronix amplifiers. A Grass camera was used to photograph tracings on a Tektronix oscilloscope. Records were obtained from experiments in which A-V block developed.

Examples of clinical electrocardiograms (ECGs) showing similar conduction ab-

normalities were selected from the files of the Heart Station of the Hahnemann Medical College and Hospital unless otherwise specified.

Results and comments

I A-V block during slow sinus or atrial rhythm. Since the levels of concealment or propagation failure in the more common varieties of second degree A-V block were previously reported¹² relatively uncommon types of A-V conduction abnormalities including advanced second degree block and multiple levels of block will be presented. Fig 1 A shows a regular 2:1 A-V conduction in the presence of a sinus rhythm averaging 113 beats per minute. Transmembrane recordings from the distal NH (node-His) region reveal a propagated action potential with an apparently normal rate of depolarization following each atrial activation or with 1:1 conduction across the A-V node. Every other NH potential is however not followed by ventricular excitation indicating a 2:1 block within the His-Purkinje system. Bizarre and wide complexes of the ventricular electrogram and a markedly prolonged His-Purkinje conduction time (160 msec) clearly show the presence of intraventricular conduction delay. Conduction time from the S-A node to the distal NH fiber measures 102 to 104

Levels of concealment in second degree and advanced second degree A-V Block

Yoshio Watanabe, M D
Leonard S Dreifus M D
Philadelphia, Pa

The effects of blocked cardiac impulses on subsequent conduction were first described by Engelmann in 1894,¹ and several experimental observations elucidated some of the underlying mechanisms early in this century.²⁻⁴ Similarly the effects of premature systole on impulse formation in the A-V junctional region were interpreted by Scherf and Shookhoff⁵ as an indication of partial retrograde penetration of the ectopic impulse. However it was after the reports of Langendorf and associates^{6,7} that the concept of concealed conduction became an indispensable tool in analyzing complex clinical arrhythmias. Later electrophysiological studies utilizing either microelectrode technique^{8,10} or close bipolar electrodes⁹ have established the validity of this concept. It should be stressed that a majority of those studies dealt with concealed conduction of premature impulses^{8,12} or impulses from the fibrillating atria^{13,14} and few such reports are available on concealment of impulses in the presence of a regular atrial or ventricular rhythm.^{8,14,16} More recently the advent of His bundle electrography has made it possible to study the phenomenon of concealed conduction

in man, and several papers^{17,18} have more fully reconfirmed the results of earlier microelectrode studies demonstrating the levels of propagation failure in various types of A-V block.¹⁵

In this paper different levels and sequences of 'concealment' in second degree and advanced second degree (where two or more impulses are consecutively blocked) A-V block are demonstrated utilizing microelectrode techniques in order to further illustrate the complexity of abnormal A-V conduction. Possible electrophysiological mechanisms underlying these varieties of A-V conduction disturbance are discussed and correlation of these experimental findings with clinical observations is attempted wherever possible.

Material and methods

Experimental studies were carried out in isolated perfused rabbit hearts using techniques of isolation and perfusion reported previously.¹⁹ We used a modified Chenoweth's solution of the following composition in millimoles per liter: NaCl 119.8, KCl 4.5, CaCl₂ 2.4, MgCl₂ 2.1, NaHCO₃ 25.0 and dextrose 10.0. The

From the Division of Cardiology, Department of Medicine and the Department of Physiology, Hahnemann Medical College Philadelphia, Pa.
Received for publication Oct. 22, 1971.
Reprint requests to Yoshio Watanabe, M.D., Department of Medicine, Hahnemann Medical College, Philadelphia, Pa. 19102.

blocked atrial impulses penetrate deeper into the A V junction the subsequent P R interval is long while impulses blocked high are followed by a shorter P R interval. They implied that concealed conduction in this case was the result of two levels of block.²¹

Considering the experimental records shown in Fig 1, the second interpretation appears more plausible as originally suggested by Katz and Pick.²¹ It should also be emphasized that the QRS duration measured 0.14 second showing intraventricular conduction delay a finding further in keeping with our experimental observations.

Another example of 2:1 A V conduction with alternation of short and long A V intervals is illustrated in Fig 3A. In this instance four cycles of 2:1 A V response are shown at the beginning of the record with the A V interval of conducted beats measuring 202, 138, 190 and 150 msec sequentially. This alternation may appear similar to that seen in Fig 1B. However a striking difference in this instance is that failure of transmission of every other atrial impulse always occurs proximal to the N fiber from which transmembrane potentials are recorded indicating intranodal block is the sole conduction disturbance. It must also be pointed out that the His Purkinje conduction time remains constant and almost normal. There is no widening of the ventricular complex in the electrogram. Thus in sharp contrast to the records in Fig 1 intraventricular conduction is not disturbed.

Although this may appear as only one level of block alternation of the A V interval still resulted from different levels of penetration into the node as suggested by the amplitude of the non propagated responses. In comparison with the local responses of the N fiber following the second and sixth atrial impulses that following the fourth impulse appears slightly greater (Fig 3A asterisk) suggesting a somewhat deeper penetration into the A V node. This causes a prolongation of the intranodal conduction time in the succeeding conducted beat (fifth atrial impulse).

Following these cycles of 2:1 response a period of 4:1 A V conduction is seen. During 4:1 conduction the second non

conducted impulse usually produces a slightly greater local response than the first and third blocked impulses. Similar sequence has been postulated in clinical ECG's which might be termed as abortive 2:1 conduction.²² It is also interesting to note that this abortive 2:1 transmission occurs when a longer A V interval is expected from the previous sequence of alternation. The long pause due to block of three successive atrial impulses is terminated by a conducted beat with a shorter A V interval. Although the transition from 2:1 to 4:1 A V conduction ratio in this instance followed an alternation of the A V interval such a transition sometimes was preceded by several cycles of 2:1 block with progressive prolongation of the A V interval in conducted beats (not shown).

In Fig 3B a record obtained three minutes after Fig 3A three cycles of 2:1 block are followed by periods of 3:1 and 4:1 A V conduction. During 2:1 conduction transmembrane record from an N (true nodal) fiber shows alternating deeper penetration of the blocked atrial impulses again associated with an alternation of the A V interval (160, 138 and 160 msec). Following a greater local response (deeper penetration of the blocked impulse) depolarization of the N fiber is slower showing a notch on phase O (arrows). Such notching of phase O or marked step formation preceding a more rapid depolarization may suggest decremental conduction or inhomogeneous conduction.²² From the preceding sequence of alternation the sixth atrial impulse is expected to show a less deep penetration. Instead this impulse again penetrates deeper as manifested by the magnitude of the local response. Block of the seventh atrial impulse causing a 3:1 conduction ratio is most likely a result of this unexpected deeper penetration of the sixth impulse. Thus in this particular instance of 3:1 conduction due to intranodal block the first blocked impulse penetrated deeper into the N region than the second. Such sequence has been termed an abortive attempt at 3:2 conduction.²²

In contrast to the pattern of 3:1 conduction in Fig 3B records obtained earlier in the same experiment showed a different sequence of 3:1 conduction (Fig 4A). In this instance 3:2 A V conduction showing

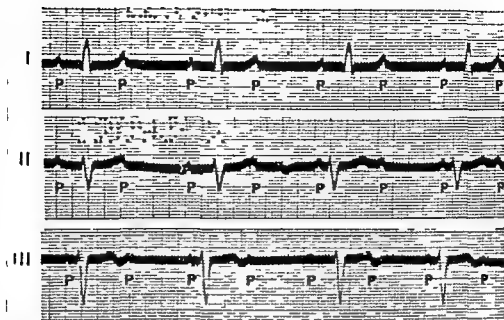


Fig 2 Clinical electrocardiogram showing 2:1 A-V conduction with widened QRS. A-V interval is either continuously long, short, or alternating. See text for discussion. (From Katz L N and Pick A. Clinical electrocardiography Part I Arrhythmias Philadelphia 1956 Lea & Febiger 1:pg 339. Reproduced with permission.)

msec. Intra atrial conduction time was 35 msec at this time (from other records). Hence intranodal conduction time was prolonged to 67 to 69 msec.

In Fig 1 B, taken 3 minutes after the record A, 2:1 A-V conduction is still present as seen in the ventricular electrogram. However, there is now alternation of short (234 msec) and long (262 to 264 msec) A-V intervals. This resulted in an alternation of the ventricular cycles. The mechanism for this alternation is apparent in the action potential recording from the NH region, where every fourth atrial beat fails to evoke a propagated response. Thus, there is 4:3 conduction across the A-V node with block of the fourth impulse above the NH fiber. Progressive prolongation of the intranodal conduction time of the Wenckebach type is evident prior to the failure of nodal transmission. However, the second of these three impulses successfully traversing the A-V node is blocked below the distal NH region as in Fig 1 A, permitting only the first and the third atrial impulses to be conducted to the ventricles. The His-Purkinje conduction time in transmission of the third atrial impulse (140 msec) is clearly longer than in the first impulse (130 msec), most probably a result of partial penetration of the second impulse into the His-Purkinje system. Following

the block of an impulse above the NH region, both the intranodal and His-Purkinje conduction times are shortened, resulting in a shorter A-V interval. Hence, alternation of short and long A-V conduction times in the presence of regular 2:1 block in this instance was caused by two levels of conduction disturbance with alternation of subnodal and intranodal block. It should be noted that the longer A-V intervals in Fig 1 B are almost identical to the A-V interval in Fig 1 A, where failure of propagation always occurred below the distal NH region. However, intranodal and subnodal conduction times are different in these two instances.

A clinical ECG with conduction phenomena similar to these experimental records is shown in Fig 2. In this instance of regular 2:1 A-V block, the P-R intervals of the conducted beats fall into two categories: one prolonged to 0.34 second and the other normal at 0.16 second. All conducted beats in Lead I show the longer P-R interval while the last three conducted beats in Lead III show alternation of short and long P-R. Katz and Pick¹ offered two alternative explanations: (1) There are two A-V conduction pathways, both of which are depressed. Both permit transmission of alternate impulses, one at a normal speed and the other at a slow speed. (2) When

6 mcs
5 mcs

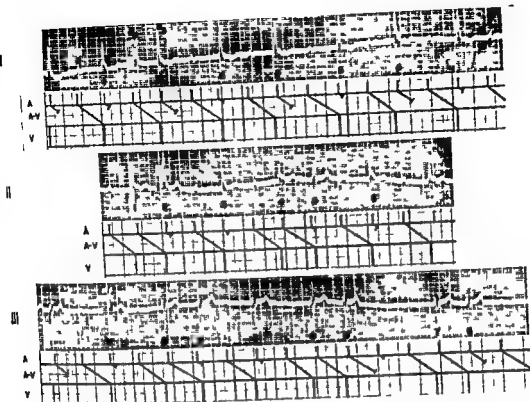


Fig 5 Electrocardiogram showing 2:1 A-V conduction with P-R alternation and 3:2 and 4:2 conduction ratios in the presence of normal QRS duration (From Landerford R *AM HEART J* 55:542 1948 Fig 7 Reproduced with permission)

turbance could actually be found in the transmembrane potential record. Following repolarization of this NH fiber after the successful propagation of the first atrial impulse the resting membrane potential is gradually decreased by what appears to be a diastolic depolarization or a step formation prior to phase 0 of the next action potential. This results in a decreased rate of phase 0 depolarization which may slow conduction in the immediately distal A-V transmission system possibly the His bundle. Hence Wenckebach periodicity in this instance can be attributed predominantly to a depressed intranodal conduction.

On the other hand Fig 4 B shows a 4:2 conduction ratio a still rarer type of advanced second degree A-V block. This is an earlier part of a long continuous record partly shown in Fig 4 A. Following transmission of two atrial impulses to the ventricles with a progressive prolongation of the A-V interval two consecutive atrial impulses are blocked within the A-V node.

The sequence of concealment is similar to that during a 3:1 conduction in Fig 4 A with the second non-conducted impulse penetrating somewhat deeper than the first. Such 4:2 conduction may sometimes follow a shortening of the A-V interval in the second conducted beat (unpublished observation).

Nevertheless Figs 3 and 4 illustrate that intranodal conduction disturbance alone can produce any A-V conduction ratio with slightly different levels of concealment including (1) 2:1 conduction with alternating short and long A-V intervals (2) transition between 2:1 and 4:1 conduction (3) 3:1 conduction mixed with 2:1 conduction (4) 3:1 conduction mixed with 3:2 conduction and (5) a 4:2 conduction ratio. That all these varieties should be and could be explained by a more comprehensive electrophysiological concept will be discussed later. Possible clinical examples of these conduction abnormalities are presented in Fig 5.

Lead I of Fig 5 shows an alternation of

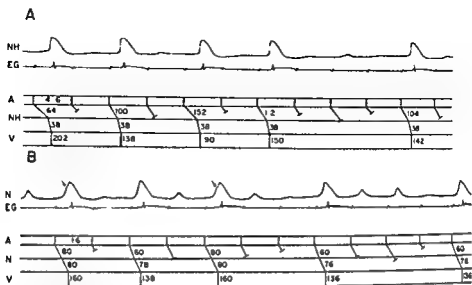


Fig. 3 *A* and *B* Transmembrane potentials from either NH region (NH) or N region (N) and an electrogram (EG) are shown. The electrogram shows both atrial and ventricular deflections. S-A nodal area is stimulated at a cycle length of 416 msec. Explanation for the ladder diagram is similar to Fig. 1. A V conduction ratios between 2:1 and 4:1 are present. See text for discussion.

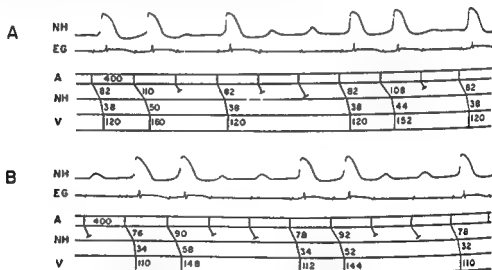


Fig. 4 *A* and *B* Records from the same experiment as in Fig. 3. 3:2 and 3:1 conduction (*A*) and 4:2 conduction ratio (*B*) are present. Abbreviations are the same as in Fig. 3. See text for discussion.

Wenckebach phenomenon alternates with a 3:1 response. During this period of 3:1 conduction, the first non-conducted impulse is blocked higher within the A-V node than the second non-conducted impulse as judged from the amplitude of local responses in a distal NH fiber. A similar sequence of progressively deeper penetration into the A-V node was previously reported during a transition from 2:1 to 3:1 conduction.¹⁵

Another point of interest in Fig. 4 *A* is the structure of the Wenckebach phenomenon. As observed in most (but not all)

examples of second degree A-V block showing such periodicity,^{15,16} prolongation of the A-V interval in the second conducted beat from 120 to 160 msec results predominantly from an increased intranodal delay as shown by a prolongation of S-A-NH interval from 82 to 110 msec (intra-atrial conduction time at this point was 28 msec). However a smaller additional conduction delay is seen below this NH fiber with the His-Purkinje conduction time increasing from 38 to 50 msec. The explanation for this additional delay in the absence of intraventricular conduction dis-

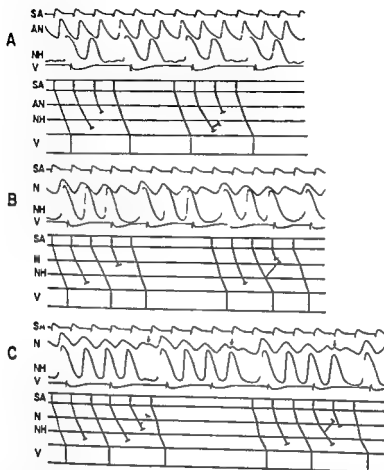


Fig 8 A B and C Various A-V conduction ratios during rapid atrial stimulation (300 per minute). Transmembrane potentials of AN region (AN) or V region (V) are recorded simultaneously with NH action potentials (NH) as well as SA and V electrograms. Sequence of A-V transmission with possible re-entry is illustrated in the diagrams. See text for detailed discussion.

may reach such a point that numerous atrial impulses are blocked consecutively. Fig. 7 shows such an example. In the initial portion of this continuous record two cycles of 2:1 conduction are seen. Marked step-formation preceding a more rapid depolarization of this N fiber in conducted beats may again suggest decremental conduction or inhomogeneous conduction.²² This period is then followed by successive block of twelve atrial impulses within the A-V node. Finally the thirteenth impulse produces depolarization of the N fiber with a less marked step formation and is successfully conducted to the ventricles. A period of 2:1 conduction is then reestablished.

It must be pointed out that in similar experimental as well as clinical records

showing prolonged periods of ventricular asystole depressed automaticity in the A-V transmission system distal to the site of block is probably present in addition to the conduction abnormality. Otherwise escape of a subsidiary pacemaker will prevent the appearance of 3:1, 4:1 or higher conduction ratios.

II A-V block during rapid atrial rhythm

It is well known that atrial flutter in man usually shows a rate of approximately 300 per minute and is most commonly associated with a 2:1 A-V conduction. The next most common conduction ratio appears to be 4:1 while any odd numbered conduction ratios are said to be rarer and are suggestive of an underlying conduction disorder. When atrial flutter was simulated in isolated rabbit hearts by electrically

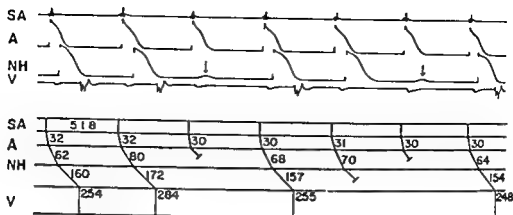


Fig 6 Same experiment as shown in Fig 1. Transmembrane potentials from a perinodal atrial fiber (A) and an NH fiber (NH) are recorded together with SA nodal (S I) and ventricular (V) electrograms. Arrows indicate non-propagated local responses in the NH region. Periods of 3:2 and 3:1 A-V conduction alternate. Detailed discussion in text.

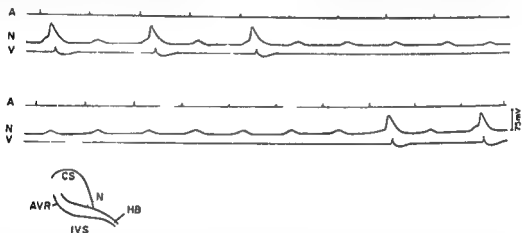


Fig 7 Intracardiac recordings showing transmembrane potentials from an N fiber (N) with atrial (A) and ventricular (V) electrograms. Inset shows a schematic diagram of the A-V junctional area. CS = ostium of coronary sinus. AVR = fibrous atrioventricular ring. HB = His bundle. IVS = interventricular septum.

short and long P-R intervals during regular 2:1 A-V block. Since the QRS is not widened and intraventricular conduction appears normal in contrast to the example shown in Fig 2, both of the two levels of concealment postulated in every other (blocked) beats must be located above the bifurcation of the His bundle, most likely within the A-V node. Hence, this ECG is analogous to the experimental record shown in the left half of Fig 3 (A and B). Furthermore, periods of 3:2 and 4:2 A-V conduction seen in Leads II and III of Fig 5 are similar to those shown in Fig 4 (A and B) respectively.

In contrast to a 3:1 A-V conduction resulting from intranodal block (Figs 3 and 4), a 3:1 response due to two distinctly different levels of block is illustrated in Fig 6 (right half), where the first non-

conducted atrial impulse is blocked below the distal NH region and probably within the His Purkinje system while the second non-conducted impulse is blocked above the NH region. This period of 3:1 response followed a period of 3:2 conduction. This record was obtained from the same experiment as shown in Fig 1. Thus, intraventricular conduction disturbance is evidenced by a prolonged His Purkinje conduction time and a widened ventricular electrogram. It must be pointed out that combined intranodal and His Purkinje block could cause (1) regular 2:1 A-V conduction with fixed or alternating P-R intervals, (2) 3:2 conduction, and (3) 3:1 conduction varieties quite similar to those produced by different levels of concealment within the A-V node alone (Figs 3 and 4).

Sometimes A-V conduction disturbance

cessive cycles and is accompanied by a gradual decrease in the action potential amplitude. This is a common finding in intranodal conduction block with Wenckebach phenomenon and is considered an expression of decremental conduction.^{12,21} However, on closer observation the fourth (the smallest) action potential of the N fiber occurs slightly earlier than is expected from the preceding sequence of depolarization. Two alternative explanations for this finding are (1) forward transmission of the atrial impulse with a shorter S-A-N conduction time (Fig 8 diagram at left) and (2) retrograde activation of the N fiber by a re-entrant impulse probably from the NH region (Fig 8 diagram at right). Since a sudden acceleration of forward conduction after an apparent increase in decrement is not readily explained, the second mechanism suggested above seems more plausible. A greater action potential amplitude accompanied by an increased rate of depolarization in the subsequent (fifth) potential may possibly be a result of slightly longer cycle lengths.

In Fig 8 C the ventricular electrogram again shows an alternation of short and long cycles. This time however the sum of short and long cycles equals five atrial intervals instead of four as seen in B. The sequence of activation in the N and NH regions and the ventricles suggests alternating 2:1 and 3:1 A-V conduction ratios (see diagrams). The period of 2:1 conduction is quite similar to the first cycle of 2:1 response in Fig 8 B in that the non-conducted impulse is blocked below the NH region (deeper penetration). The third atrial impulse is therefore conducted to the ventricles with a prolonged A-V interval. In contrast to the sequence seen in B the fourth atrial impulse again penetrates deep into (or beyond) the NH region and is blocked within the His-Purkinje system. This is followed by block of the fifth impulse above the NH fiber resulting in a 3:1 conduction ratio. Such transition from 2:1 to 3:1 conduction closely resembles that in Fig 3 B recorded in the presence of a slower atrial rhythm.

The transmembrane potential from the A fiber again suggests a progressively increasing decrement in five successive depolarizations with the sixth action poten-

tial showing a greater amplitude and a more rapid phase 0 depolarization. Three groups of five action potentials are thus shown in this figure as compared to the groups of four N potentials in Fig 3 B. In this instance however either the fifth (in the first group) or the fourth (in the second and third group) N potential of a group shows a distinct notch or doubly peaked appearance (arrow). The most likely explanation for this finding is a re-entry movement from the area distal to this N fiber as illustrated in the diagram. When the fourth action potential is doubly peaked (diagram at right) the fifth potential shows a further reduction in the amplitude and the rate of depolarization but without a notch. The NH recording then shows no signs of electrotonic spread following the fourth action potential. Thus the fifth atrial impulse here appears blocked immediately distal to this N fiber. When the fifth N potential has double peaks on the other hand there is a small local response of the NH fiber after its fourth action potential (a terisk). A slightly deeper penetration of the fifth atrial impulse possibly due to the absence of re-entry of the preceding impulse may have caused deeper penetration and reciprocation of this impulse (diagram at left). However this interpretation may impose some difficulty in explaining the better N potential seen in the subsequent (sixth) depolarization since the period for recovery in this fiber apparently is even shorter than in the preceding cycles. Possible mechanisms for such findings will be discussed later.

Nevertheless these observations indicate that the sequence of concealment in these various conduction ratios is essentially identical in the presence of both slow and more rapid atrial mechanisms although the actual levels of block may be different in individual cases. Furthermore it is interesting to note the relationship between grouping of NH action potentials and A-V conduction ratio during the simulated atrial flutter. When the NH recording shows grouping of two action potentials a 3:1 conduction may result grouping of three action potentials could cause a 2:1 conduction with alternating short and long A-V intervals and grouping of four action potentials is associated with alternation of

stimulating the right atrium at similar frequencies 2:1 A-V block commonly appeared. In such instances every other atrial impulse was usually blocked within the A-V node, causing a 2:1 response in the distal NII region (not shown). Fig. 8 illustrates less common varieties of conduction observed in one of these experiments.

In Fig. 8, A the atrial electrogram recorded from the S-A nodal region reveals a rate of 300 per minute while the ventricular electrogram shows a rate of 100 per minute, indicating a 3:1 A-V conduction. The presence of 1:1 response in the AN (atrionodal) region is clearly seen in the intracellular record designated AN, although a decrease in the rate of phase 0 depolarization is apparent. On the other hand the transmembrane potentials recorded from an NII fiber show two propagated action potentials followed by a pause. The first NII potential appears relatively normal in configuration, and is accompanied by ventricular excitation. There is an increased delay between activation of the AN and NII fibers in transmission of the second atrial impulse. The second NII action potential starts from a lower membrane potential and shows a markedly reduced rate of depolarization, probably due to incomplete recovery of excitability in this region. This impulse is then blocked below this NII fiber and ventricular excitation does not follow. Such failure of subnodal propagation may have resulted from a reduced efficiency of these NII action potentials in exciting the immediately distal A-V transmission system or the His bundle. It is well known that any cause which reduces the action potential amplitude and the rate of phase 0 depolarization could produce a decreased conduction velocity and decrement.²⁴ Thus, the level of block of this second impulse most probably is in the main His bundle. An alternative explanation is that, due to a lower frequency of "effective" impulses invading the His-Purkinje system (100 per minute), the duration of action potential and refractory period in the His-Purkinje fibers during successful transmission of the first atrial impulse is prolonged, causing a refractory barrier to the second impulse below the NII region.

In contrast the third atrial impulse is

blocked above this NII fiber, possibly because of a progressively increasing decrement within the A-V node as commonly seen in Wenckebach type of second degree block.²⁵ Hence 3:1 A-V conduction in this instance is associated with a deeper penetration of the first and a less deep penetration of the second non-conducted impulse. This sequence is similar to that seen in Fig. 6 although the levels of concealment might be different. The small undulations seen following the second NII action potential are probably electrotonic spread from either forward penetration of the third atrial impulse or an attempted reciprocation (re-entry) of the second impulse below this NII fiber, or both (see diagrams below Fig. 8, 1).

Fig. 8, B and C, are different portions of a long continuous record obtained 15 minutes prior to the recording of A. Transmembrane potentials are recorded from an N fiber and an NII fiber slightly more distal to the NII fiber in Fig. 8, 1. In portion of the ventricular electrogram in B reveals an alternation of long and short cycles the sum of which corresponds to four atrial intervals. Transmembrane action potentials from the N fiber show an apparent 1:1 response to the atrial impulses while a group of three NII potentials is regularly followed by a pause. A progressively increasing conduction delay appears to be present between the N and NII fibers, although the onset of depolarization cannot be precisely determined in these slowly rising action potentials. The sequence of A-V conduction is interpreted as shown in the diagram, i.e. a 2:1 conduction with alternating short and long A-V conduction time. This is quite similar to the observations made in the presence of a slower atrial rhythm (Fig. 1B) since a longer A-V interval follows a blocked impulse with deeper penetration (to or beyond the distal NII region) while a shorter A-V interval follows the block of an impulse at a higher level (above the NII region). In both instances groups of three propagated responses are seen in the distal NII region.

Although every atrial depolarization appears to be followed by an action potential in the N fiber, the rate of phase 0 depolarization is progressively decreased in four suc-

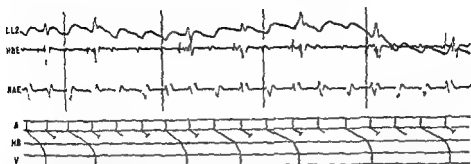


Fig. 10 Simultaneous recordings of the standard Lead II (LL2), His bundle electrogram (HBE) and right atrial electrogram (RAE) in a patient with atrial flutter and varying conduction ratios similar to Fig. 9 B. The ladder diagram shows period of 2:1 and 3:1 A-V conduction. Note that every QRS complex is preceded by a His deflection with essentially identical H-Q interval but no His potential is seen following a right atrial excitation that is not conducted to the ventricles. Some of the oblique lines representing concealed conduction are dotted as the depths of penetration cannot be judged from the His bundle recording.

atrial and ventricular excitation is available the designation of upper and lower A-V junction may be somewhat misleading. Today when His bundle electrograms are available the A-V transmission system may be conveniently divided into the portions above and below the His bundle recording site which may enable us to identify different sites of conduction disturbance in certain selected cases. However it must be stressed that many theoretical deductions made from the ECG analyses alone have previously been confirmed by various investigators particularly with the use of premature stimulation or other experimental conditions favoring the occurrence of concealed conduction.¹⁴

On the other hand several examples of second degree A-V block with different and sometimes multiple levels of delay and propagation failure have been reported from our laboratory.^{15,16} Other less common varieties of A-V block discussed in the present study further illustrate multiple levels of concealment in the A-V transmission system. For instance Figs. 1 and 6 clearly indicate that when an intraventricular conduction disturbance is present two levels of block can develop one within and the other below the A-V node. It is therefore reasonable to assume that a clinical tracing as shown in Fig. 2 resulted from a combination of intranodal and His-Purkinje block. In contrast multiple levels of block could develop entirely within the A-V node in the presence of normal intraventricular conduction (Figs. 3 and 4). In these instances depths of intranodal pene-

tration may be judged from the size of local responses.^{17,18} Hence when two levels of concealment are postulated in an ECG showing normal QRS complexes (Fig. 3) conduction disturbance is most probably confined within the A-V node but showing variation in the depths of penetration.

Another variety of two levels of concealment in the presence of normal intraventricular conduction involves block within the A-V node and that below—probably in the main His bundle (Fig. 8). When an impulse decrements sufficiently within the A-V node but is still capable of traversing the critical N region the resultant action potential in the NH region may show a decreased amplitude and rate of depolarization. Such NH potentials may be inefficient to fully activate the His bundle resulting in failure of propagation within this latter structure. Here again however an increased decrement in the A-V node appears to play a major role.

The effects of refractoriness in the more distal regions of the A-V conduction system in preventing propagation of some impulses which traversed the A-V node have been pointed out with reference to Fig. 8.1. Once the number of impulses reaching subnodal regions is reduced due to the development of second degree intranodal block resultant longer cycle lengths could cause a prolongation of the refractory period in fibers of the His-Purkinje system and blockage of the immediately succeeding atrial impulse particularly when atrial rate is rapid as in flutter. This mechanism may explain formation of an additional

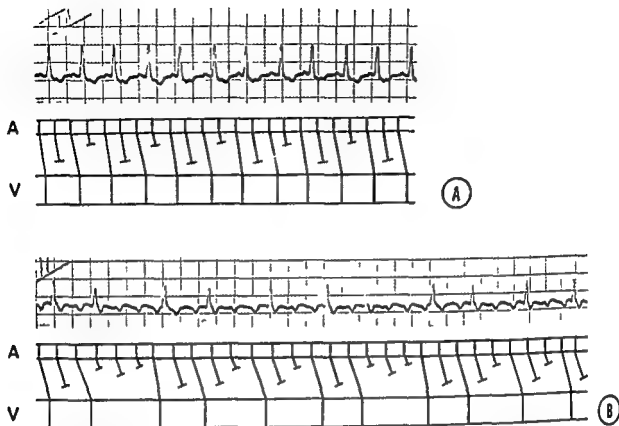


Fig 9 *A* and *B* Electrocardiograms (Lead II) from two patients with atrial flutter. Regular 2:1 AV transmission with alternation of short and long AV intervals (*A*) and varying conduction ratios ranging from 2:1 to 4:1 (*B*) are shown.

2:1 and 3:1 conduction ratios (Fig 8 *A*, *B*, and *C* respectively). It is conceivable that, when conductivity in the subnodal region is more normal, these groupings of NH action potentials may result in 3:2, 4:3, and 5:4 AV conduction ratios. In the latter case, there will be only one level of concealment.

Fig 9 illustrates clinical examples of atrial flutter with these several conduction ratios. In *A*, a Lead II electrocardiogram shows regular undulations of the baseline at the rate of 320 per minute, indicating flutter. There is alternating short and long ventricular cycles with an average ventricular rate of 160 per minute. This must be interpreted as 2:1 AV conduction with alternation of deeper and less deep penetration of the non-conducted atrial impulses, a clinical counterpart of what was shown in Fig 8 *B*. In part *B* of Fig 9, a Lead II recorded from a different patient, AV conduction ratios ranging from 2:1 to 4:1 are seen as diagrammed below. Various sequences of partial penetration in this tracing may well be considered similar to those seen in Fig 8, *A* and *C*. In these clinical cases of

atrial flutter, however, it cannot readily be determined whether those impulses penetrating deeper into the AV junction did partially invade the His bundle or were blocked within the NH region. A His bundle electrogram recorded in a similar patient (Fig 10) failed to supply such information.

That multiple levels of concealment are also seen in retrograde transmission in the presence of so-called ventricular tachycardia has previously been reported.¹⁵

Discussion

In his original article on concealed conduction, Langendorf⁶ already postulated different depths of penetration into AV junction of the blocked impulses in order to explain variation of the subsequent P-R interval. Later, two levels of concealment were often referred to as "upper and lower portions of the AV junction, especially in the presence of AV junctional impulse formation or atrial flutter."²⁴ Although such arbitrary subdivision of the AV transmission system is inevitable in clinical electrocardiography where only information on

non-conducted impulse. Such sequence of concealment has indeed been observed on several occasions where the first non-conducted impulse was blocked in the His-Purkinje system (Fig 6 and Fig 8 A) or blocked within the A V node (Fig 3 B). However other records with intranodal block showed an opposite sequence or a deeper penetration of the second nonconducted impulse than the first (Fig 4 A and Fig 6 in reference 15). This indicates that the concept of concealed conduction simply leaving the state of refractoriness in its wake may not adequately explain all similar conduction ratios. Furthermore, when a transition from 2:1 conduction with alternating short and long P-R interval to 3:1 conduction was observed in a clinical example (Fig 8 in reference 7) a 3:1 ratio followed a shorter P-R interval. In contrast in our Fig 3 B the period of 3:1 conduction followed a longer A-V conduction time of the alternating intervals. Even those rare instances of 4:2 A-V conduction were associated with either progressive prolongation (Fig 4 B) or with shortening (unpublished observation) of the A-V interval prior to the blockage of two successive impulses.

Although these contrasting patterns of conduction may appear insignificant they bring into sharp focus the complexity of abnormal A-V conduction. It further emphasizes the fact that a more universal explanation is needed for the many varieties of A-V block by incorporating numerous mutually interrelated mechanisms rather than what was originally implied by concealed conduction.¹¹ Since a detailed discussion of all these mechanisms is beyond the scope of this paper and will be presented elsewhere,¹² only several factors pertinent to the present study are discussed.

It is well known that the A-V conducting system comprises a series of fiber types having different electrophysiological properties. For example the atrial A-V nodal and His-Purkinje fibers show marked differences in their action potential characteristics¹³ and in their response to the same physiological or pharmacological factors.^{14,15} Furthermore any change in the excitation process occurring in proximal fibers would alter the strength of stimuli

and thus indirectly affect depolarization of distal fibers. Several investigators showed that both the direction and strength of the excitation front could affect A-V nodal transmission.^{11,16} This is partly explained by the anatomy of A-V nodal tissues where a marked variability in diameter and length of fibers exists with a complex network.¹⁴ Within this net-like structure of the A-V node transmission of impulses is further complicated by local differences in excitability particularly under abnormal conditions. This could result in an irregular fragmented excitation front which is less effective in exciting the more distal tissue. Such inhomogeneous conduction within the A-V node culminating in unidirectional block and re-entry of an impulse was reported earlier.¹⁷ Similar findings were later reported by other investigators utilizing premature atrial stimulation.¹⁸ Once re-entry occurs in the A-V junctional tissue it would possibly leave non-uniform areas of refractoriness or excitability affecting the wave front of subsequent impulses. Depending on the location and extent of the re-entry movement and also on the presence or absence of areas participating neither in forward nor in retrograde transmission (bidirectional block) the succeeding wave of excitation may become either more fragmented or reorganized. Thus conduction is further depressed in some instances while it is improved in others. This may explain the apparent paradox of 3:1 conduction with progressively deeper penetration of the two blocked impulses (Fig 4 A and Fig 6 reference 15) in contrast to successively less deep penetration in 3:1 conduction (Fig 3 B). Furthermore the observation of a better action potential immediately following an apparent re-entry movement (Fig 8 C sixth N potential in the left diagram) may be explained by this concept.

In addition to inhomogeneity of conduction temporal fluctuations of conductivity must also be considered. In any depressed tissue with reduced membrane potential and decreased rate of phase 0 depolarization (especially in the V region of the A-V node) the safety factor for conduction may be marginal. Hence it is possible that with only minor variations in coronary flow and oxygen supply^{19,20} vagal tone^{21,22} or other

level of conduction block below the A V node, when no underlying intraventricular conduction disturbance is present. Such interpretation may be supported by the fact that (1) the action potential duration becomes progressively prolonged from the atrial fibers through the A V node² and down to the peripheral Purkinje fibers³ and (2) the effects of altered cycle lengths on the action potential duration are most pronounced in the Purkinje system.^{24,27} Concealment of some impulses within the right bundle branch system resulted from this mechanism, when several premature atrial stimuli were applied in rapid succession.¹¹

Operation of a similar mechanism may also be invoked in the presence of a slower atrial rhythm. In Fig. 6, for instance, block of the fifth atrial impulse below the NH region may possibly be explained by a prolonged refractory period in the His Purkinje system due to a long preceding cycle (greater than 1000 msec) caused by intranodal block of the third impulse. This would imply a prolongation of the effective refractory period to 520 msec or longer. This marked prolongation may not be common but is seen under certain conditions.²⁷ If we accept this possibility in maintenance of a regular 2:1 block at the His Purkinje level as seen in Fig. 1A from the same experiment can be explained on the same basis. On the other hand one might theoretically expect still a longer duration of refractoriness in the His Purkinje system after a period of 3:1 conduction (Fig. 6 right). This should tend to perpetuate a 3:1 response, or at least 2:1. However 3:1 conduction alternated with a 3:2 conduction for several cycles in the remaining portion of this continuous record. This may suggest operation of mechanisms other than refractoriness. Incremental conduction at the bundle branch level may not be ruled out as a possibility since underlying intraventricular conduction disturbance is evident in this instance.

The role of refractoriness has also been suggested in a different manner in the presence of atrial flutter.⁷ Langendorf and Pick⁷ postulate that, when the atrial rate is quite rapid (e.g., 300 per minute) every other impulse will arrive at the A V junction during its refractory period and hence is

ineffective to excite the junctional tissue. This reduces the number of impulses invading (and usually traversing) the A V junction to one half the flutter rate (150 per minute). If intranodal conduction is now depressed, some of these invading impulses are blocked, often causing a 4:1 response. They term these mechanisms as two levels of "impedance," one at a higher level and due to physiological interference and the other at a lower level due to abnormal conduction block.⁷ It is obvious that the term "physiological interference" as used by these authors represents failure of propagation as a result of refractoriness. These authors further argue that in these more common varieties of A V conduction ratios (2:1 and 4:1) during atrial flutter, concealed conduction does not have to be invoked. The following comment appears pertinent regarding the definition of concealed conduction.

According to Langendorf and Pick,⁷ concealed conduction "consists of incomplete penetration of preformed conduction pathways by an apparently blocked impulse. It manifests itself by its effect upon conduction or formation of a subsequent forward or retrograde impulse." It seems that many electrophysiologists regard the first part of the above statement as the sole criterion for concealed conduction.^{8,12} In that case any impulse blocked within the A V transmission system should constitute an example of concealed conduction, whether it manifests itself or not. Strictly speaking, however, no 'concealment' exists in electrophysiological studies utilizing microelectrodes as direct recording of those blocked impulses is possible. Furthermore, the original definition of concealed conduction as quoted above⁷ has been widely accepted. Hence, the word 'concealed conduction' should be reserved for clinical electrocardiography and should include its manifestation by its effects on conduction or formation of a subsequent impulse while partial penetration into the A V transmission system may be a more acceptable term in electrophysiological studies.

The mechanism of the 3:1 conduction ratio has been explained by a deeper penetration of the first non-conducted impulse which produces more refractoriness of the A V junction⁸ and thus blocks the second

cycling starts again. In other words regular alternation of short and long A V intervals with 2:1 A V response resulted from this particular intranodal conduction ratio—i.e. 4:3.

The above explanation is further supported by the finding in Fig. 11 a record obtained 4 minutes after Fig. 1B. Here intranodal conduction is slightly more depressed resulting in a 3:2 conduction ratio. Every third atrial impulse is now blocked within the A V node. Whether both of the two NH responses could traverse the His-Purkinje system may then depend on slight fluctuation of subnodal conductivity or duration of refractoriness in Purkinje fibers or both. The possible role of the refractory period in this record has already been discussed. Thus a 3:2 intranodal conduction results either in 3:2 or 3:1 A V response (Fig. 6). Later in this experiment only 2:1 intranodal block was observed indicating further deterioration of the intranodal conduction (not shown). Although this should result in a constant shorter A V interval the expected shortening of conduction time was not apparent because of a progressive depression of conduction throughout the A V transmission system. It should be re-emphasized that a similar relationship between the intranodal conduction ratios (or number of NH responses) and the A V conduction ratios (or number of ventricular responses) was clearly seen in the presence of a rapid atrial mechanism (Fig. 8).

Finally the values and limitations of His bundle recordings during A V block may deserve a brief comment. If the impulses blocked below the distal NH region in Figs. 1 and 6 are conducted through the main His bundle but blocked at the bundle branch level His electrograms would yield the same information as obtained in these experimental studies. Similarly if those impulses blocked below the NH region in Fig. 8 did invade but decrement within the main His bundle as postulated above a His electrogram recorded from an appropriate site may reveal an attenuated deflection suggesting decremental conduction. In such a case His bundle recordings will be of value in localizing the level of block and in demonstrating the effects of concealed conduction. However His bundle

electrograms recorded from a similar clinical case (atrial flutter with 2:1 3:1 and 4:1 A V conduction) failed to show any evidence of partial penetration into the His bundle (Fig. 10). Therefore whether some of the blocked impulses penetrated deeper or not could not be judged from this recording. It should also be pointed out that even when an attenuated His deflection is recorded extreme caution must be exercised to rule out the possibility of temporary catheter displacement before decremental conduction is invoked. Furthermore His bundle electrograms would not supply information on the different levels of concealment within the A V node (Figs. 3 and 4) nor would it reveal any evidence for intranodal re-entry (Fig. 8). Despite these obvious limitations His bundle recordings would still prove a useful clinical tool in studying certain selected cases of abnormal A V transmission.

Summary

Different levels and sequences of propagation failure within the A V transmission system in the presence of second degree and advanced second degree A V block were demonstrated in isolated perfused rabbit hearts utilizing the microelectrode techniques. Alternation of short and long A V conduction time during a regular 2:1 A V block was shown to result from alternation in the depths of penetration of non-conducted impulses into the A V junctional tissues. A 3:1 A V conduction ratio resulted either from (1) subnodal block of the first non-conducted impulse followed by intranodal block of the second non-conducted impulse or (2) intranodal block of two consecutive impulses with either deeper or less deep penetration of the first non-conducted impulse as contrasted to the second. The first variety was observed either with wide QRS complexes (disturbed intraventricular conduction) or with normal QRS duration (normal intraventricular conduction) while the second variety was associated with normal intraventricular conduction. Transition between various conduction ratios including 2:1 3:1 4:1 3:2 and 4:2 was observed and multiple intranodal concealment was also demonstrated. Similarities of the sequence of partial penetration in both slower sinus

physiological factors, propagation of impulses may fail at one moment but may barely succeed at the next. It will be readily understood that combination of these two factors (spatial inhomogeneity and temporal fluctuations of conductivity) could produce any sequence and ratio of conduction. Thus, such a term as "abortive attempt at 2:1 and 3:2 conduction"^{7,1} may have a practical value in describing certain conduction phenomena, but may not reveal the precise physiological mechanisms.

On the other hand, some comment is necessary regarding the so-called dual A-V transmission system. The early physiological observations suggesting the presence of two functional pathways³⁹ were subsequently explained by interactions between intranodal conduction time and recovery of excitability in the His-Purkinje system,⁴⁰ and therefore may not be pertinent in the present discussion. However, a similar concept may still be applicable in certain conduction phenomena as shown in Figs 1 and 2. One of the explanations of Fig 2 given by Katz and Pick²¹ invokes two pathways with different conduction velocities. When impulses are transmitted through the two pathways alternately, an alternation of short and long P-R intervals will result while transmission through only one of the pathways will cause a constant (either long or short) P-R interval. If we assume that such dual pathways are located entirely within the A-V nodal tissue, alternation of short and long P-R intervals must necessarily be accompanied by an alternation of short and long intranodal conduction times with essentially no change in subnodal (His-Purkinje) conduction. Assumption of dual pathways located below the A-V node would result in an opposite sequence of events. Our experimental observations in Fig 1, however, do not confirm these explanations. During alternation of short and long A-V intervals (Fig 1B), there was a progressive prolongation of intranodal conduction time in the form of Wenckebach periodicity, causing a 4:3 response in the distal NH region. Intranodal block of an impulse was followed by a shortening of both intranodal and His-Purkinje conduction time. Furthermore, the period of 2:1 conduction with a fixed long A-V interval (Fig 1A) was associated

with a short (not long) intranodal conduction time but always with a deep penetration of the blocked atrial impulses into subnodal regions. A little later in the same experiment, periods of 3:2 and 3:1 A-V conduction were observed (Fig 6), with a still longer A-V conduction time during a 3:2 ratio. Similar conduction phenomena in the presence of intranodal block alone were also associated with alternation of the depths of penetration (Fig 3). Thus, at least in these particular experiments, no evidence of dual A-V pathways was suggested. Hence, different depths of penetration due to fluctuations of conductivity as discussed above appears the most plausible explanation. A similar statement was originally made by Katz and Pick.¹

Regarding the transition from Fig 1A to Fig 1B, the following interpretation may be proposed. Although conduction was depressed in both the A-V node and the His-Purkinje system, transmission of impulses was more critical in the latter tissue initially. The A-V node was still capable of 1:1 transmission as seen in action potentials from the NH fiber. If a single impulse fails to be propagated below the NH region, perhaps due to slight fluctuations in conductivity, a resultant longer interval below the site of block may prolong the duration of action potential and refractoriness in His-Purkinje fibers. When such prolongation reaches a value similar to the atrial cycle length, an impulse following upon a conducted beat may encounter such a refractory barrier and be blocked again subnodally. This sequence would tend to sustain periods of 2:1 conduction at the His-Purkinje level (Fig 1A). Subnodal conduction time remains prolonged partly as a result of repeated partial penetration of the His-Purkinje system by nonconducted impulses. Subsequently, intranodal conduction becomes further depressed and a Wenckebach phenomenon with eventual failure of propagation develops. When intranodal conduction shows a 4:3 response as in Fig 1B, every fourth impulse is blocked within the A-V node instead of the His-Purkinje system while every second impulse is still blocked subnodally. Following block of an impulse within the A-V node, shortening of conduction time occurs both within and below the node and thus

- Excitation sequences of the atrial septum and the AV node in isolated hearts of the dog and rabbit *Circ. Res.* 29:156 1971
- 34 Truex R C Anatomical considerations of the human atrioventricular junction in Dreifus L S and Likoff W editors Mechanisms and therapy of cardiac arrhythmias New York 1966 Grune and Stratton pp 333 340
- 35 Mendez C and Moe G K Demonstration of a dual AV nodal conduction system in the isolated rabbit heart *Circ Res* 19 3:8 1966
- 36 Watanabe, Y and Dreifus L S Effects of coronary flow on atrioventricular conduction *Fed. Proc* 29 588 1970 (abstract)
- 37 Matsuda K, Hoshi T and Kameyama S Action of acetylcholine and adrenaline upon the membrane potential of the atrioventricular node (Tawara) *Tohoku J Exp Med* 68 16 1958
- 38 Craneheld P F Hoffman B F and Paes de Carvalho A The effect of acetylcholine on single fibers of the AV node *Circ Res* 7 19 1959
- 39 Moe G K, Preston J H and Burlington H Physiologic evidence for a dual AV transmission system *Circ Res* 4:357 1956
- 40 Hoffman B F, Moore E N, Stuckey J H et al Functional properties of the atrioventricular conduction system *Circ Res* 13:308 1963
- 41 Narula O S and Samet P Wenckebach and Mobitz type II AV block due to block within the His bundle and bundle branches *Circulation* 41 947 19 70

or atrial rhythms and rapid atrial rhythm simulating atrial flutter were illustrated, and possible electrophysiologic mechanisms for these conduction phenomena were discussed. Clinical examples of these varieties of A-V conduction disturbance were presented, suggesting applicability of these experimental observations to the interpretation of surface ECG's.

The authors are most grateful to Drs. Richard Langendorf and Alfred Pick for their kind permission to use figures from their previous publications.

REFERENCES

- 1 Engelmann T W Beobachtungen und Versuche am suspendierten Herzen Pflügers Arch 56 119 1894
- 2 Ashman R Conductivity in compressed cardiac muscle I The recovery of conductivity following impulse transmission in compressed auricular muscle of the turtle heart Am J Physiol 74 121 1925
- 3 Drury A N Further observations upon intra-auricular block produced by pressure or cooling Heart 12 143 1925
- 4 Lewis F and Master A M Observations upon conduction in the mammalian heart A-V conduction Heart 12 209 1925
- 5 Scherf D and Shookhoff C Reizleitungsstörungen im Bündel I Mitteilung Über Veränderungen des atrioventrikulären Rhythmus durch Extrasystolen Wien Arch Inn Med 10 97 1925
- 6 Langendorf R Concealed A-V conduction The effect of blocked impulses on the formation and conduction of subsequent impulses Am Heart J 35 542 1948
- 7 Langendorf R and Pick A Concealed conduction Further evaluation of a fundamental aspect of propagation of the cardiac impulse Circulation 13 381 1956
- 8 Hoffman B F Cranefield P I and Stuckey J H Concealed conduction Circ Res 9 194 1961
- 9 Moe G K Abildskov J A and Mendez C An experimental study of concealed conduction Am Heart J 67 338 1964
- 10 Moe G K Mendez C and Abildskov J A A complex manifestation of concealed A-V conduction in the dog heart Circ Res 15 51 1964
- 11 Moore E N Microelectrode studies on concealment of multiple premature atrial responses Circ Res 18 660 1966
- 12 Moore E N Microelectrode studies on retrograde concealment of multiple premature ventricular responses Circ Res 20 88 1967
- 13 Moore E N Observations on concealed conduction in atrial fibrillation Circ Res 21 201 1967
- 14 Yamada K Okayama M Hori K et al On the genesis of the absolute ventricular arrhythmia associated with atrial fibrillation Circ Res 22 107 1968
- 15 Watanabe Y and Dreifus L S Second degree atrioventricular block Cardiovasc Res 1 150 1967
- 16 Watanabe Y A-V conduction disturbances and electrophysiology Igaku no Asumi 339 1969 (In Japanese)
- 17 Damato A N Lau S H Helfant R H et al A study of heart block in man using His bundle recordings Circulation 39 797 1969
- 18 Narula O S Lister J W Hildner F I et al Localization of A-V conduction defects in man by recording of the His bundle electrogram Am J Cardiol 25 228 1970
- 19 Kosen K M Loch H S Chuquimima R et al Site of heart block in acute myocardial infarction Circulation 42 925 1970
- 20 Watanabe Y and Dreifus L S Sites of impulse formation within the atrioventricular junction of the rabbit Circ Res 22 17 1968
- 21 Katz L N and Park A Clinical electrocardiography Part I Arrhythmias Philadelphia 1956 Lea & Febiger
- 22 Watanabe Y and Dreifus L S Inhomogeneous conduction in the A-V node A model for reentry Am Heart J 70 505 1965
- 23 Hoffman B F and Cranefield P I Electrophysiology of the Heart New York 1960 McGraw Hill Book Co
- 24 Langendorf R Pick A Edelist A et al Experimental demonstration of concealed A-V conduction in the human heart Circulation 32 386 1965
- 25 Watanabe Y and Dreifus L S Electrophysiologic effects of digitalis on A-V transmission Am J Physiol 211 1461 1966
- 26 Moore E N Ireston J B and Moe G K Duration of transmembrane action potentials and functional refractory periods of canine feline tendon and ventricular myocardium Circ Res 17 159 1965
- 27 Watanabe Y Purkinje repolarization as a possible cause of the U wave in the electrocardiogram Fed Proc (Abstr) 31 313 1972
- 28 Watanabe Y and Dreifus L S Factors determining atrioventricular conduction (In preparation)
- 29 Watanabe Y and Dreifus L S Interactions of quinidine and potassium on atrioventricular transmission Circ Res 20 434 1967
- 30 Watanabe Y Effects of electrolytes and antiarrhythmic drugs on atrioventricular conduction in Sandoe E Flested Jensen I and Oleen K H editors Symposium on cardiac arrhythmias Södertälje Sweden 1970 AB Astra pp 535 557
- 31 Paes de Carvalho A Cellular electrophysiology of the atrial specialized tissues in Paes de Carvalho A De Mello W C and Hoffman B F editors The specialized tissues of the heart Amsterdam 1961 Elsevier Publishing Co pp 115 150
- 32 Janse M J Influence of the direction of the atrial wavefront on A-V nodal transmission in isolated hearts of rabbits Circ Res 25 459 1969
- 33 Spach M S Lieberman M Scott J G et al

- Excitation sequences of the atrial septum and the AV node in isolated hearts of the dog and rabbit *Circ. Res.* 29 156 1971
- 34 Truex, R. C. Anatomical considerations of the human atrioventricular junction in Dreifus L. S. and Likoff W. editors *Mechanisms and therapy of cardiac arrhythmia* New York, 1966 Grune and Stratton pp 333-340
- 35 Mendez C. and Moe G. H. Demonstration of a dual AV nodal conduction system in the isolated rabbit heart *Circ. Res.* 19 378 1966
- 36 Watanabe Y. and Dreifus L. S. Effects of coronary flow on atrioventricular conduction *Fed. Proc.* 9 588 1970 (abstract)
- 37 Matsuda K., Hoshi T. and Kameyama S. Action of acetylcholine and adrenaline upon the membrane potential of the atrioventricular node (Tawara) *Tohoku J. Exp. Med.* 68 16 1958
- 38 Cranefield I. F., Hoffman B. F. and Paes de Carvalho A. The effect of acetylcholine on single fibers of the AV node *Circ. Res.* 19 1959
- 39 Moe G. H., Preston J. B. and Burlington H. Physiologic evidence for a dual AV transmission system *Circ. Res.* 4 357 1956
- 40 Hoffman B. F., Moore E. N., Stuckey J. H. et al. Functional properties of the atrioventricular conduction system *Circ. Res.* 13 308 1963
- 41 Narula O. S. and Samet P. Wenckebach and Mobitz type II AV block due to block within the His bundle and bundle branches *Circulation* 41 917 1970

or atrial rhythms and rapid atrial rhythm simulating atrial flutter were illustrated and possible electrophysiological mechanisms for these conduction phenomena were discussed. Clinical examples of these varieties of A-V conduction disturbance were presented, suggesting applicability of these experimental observations to the interpretation of surface ECG's.

The authors are most grateful to Drs. Richard Langendorf and Alfred Pick for their kind permission to use figures from their previous publications.

REFERENCES

- Engelmann T W. Beobachtungen und Versuche am suspendierten Herzen. *Flügers Arch* 56:149, 1894.
- Ashman R. Conductivity in compressed cardiac muscle. I. The recovery of conductivity following impulse transmission in compressed auricular muscle of the turtle heart. *Am J Physiol* 74:121, 1925.
- Drury A N. Further observations upon intra-auricular block produced by pressure or cooling. *Heart* 12:143, 1925.
- Lewis T and Master A M. Observations upon conduction in the mammalian heart. A-V conduction. *Heart* 12:209, 1925.
- Scherf D and Shookhoff C. Reizleitungsstörungen im Bündel I. Mitteilung Über Veränderungen des atrioventrikulären Rhythmus durch Extrasystolen. *Wien Arch Inn Med* 10:97, 1925.
- Langendorf R. Concealed A-V conduction. The effect of blocked impulses on the formation and conduction of subsequent impulses. *Am Heart J* 35:542, 1948.
- Langendorf R and Pick A. Concealed conduction. Further evaluation of a fundamental aspect of propagation of the cardiac impulse. *Circulation* 13:381, 1956.
- Hoffman B I, Cranefield P F and Stuckey J H. Concealed conduction. *Circ Res* 9:194, 1961.
- Moe G K, Abildskov J A and Mendez C. An experimental study of concealed conduction. *Am Heart J* 67:338, 1964.
- Moe G K, Mendez C and Abildskov J A. A complex manifestation of concealed A-V conduction in the dog heart. *Circ Res* 15:51, 1964.
- Moore E N. Microelectrode studies on concealment of multiple premature atrial responses. *Circ Res* 18:660, 1966.
- Moore E N. Microelectrode studies on retrograde concealment of multiple premature ventricular responses. *Circ Res* 20:88, 1967.
- Moore E N. Observations on concealed conduction in atrial fibrillation. *Circ Res* 21:201, 1967.
- Yamada K, Okajima M, Hon K, et al. On the genesis of the absolute ventricular arrhythmia associated with atrial fibrillation. *Circ Res* 22:107, 1968.
- Watanabe Y and Dreifus L S. Second degree atrioventricular block. *Cardiovasc Res* 1:150, 1967.
- Watanabe Y. A-V conduction disturbances and electrophysiology. *Igaku no Asynun* 69:339, 1969. (In Japanese).
- Damato A N, Liu S H, Helfant R H, et al. A study of heart block in man using His bundle recordings. *Circulation* 39:797, 1969.
- Narula O S, Fister J W, Hildner F J, et al. Localization of A-V conduction defects in man by recording of the His bundle electrogram. *Am J Cardiol* 25:728, 1970.
- Rosen K M, Loeb H S, Chuquimima R, et al. Site of heart block in acute myocardial infarction. *Circulation* 12:975, 1970.
- Watanabe Y and Dreifus L S. Sites of impulse formation within the atrioventricular junction of the rabbit. *Circ Res* 22:17, 1968.
- Katz L N and Pick A. Clinical electrocardiography. Part I. Arrhythmias. Philadelphia, 1956. Lea & Febiger.
- Watanabe Y and Dreifus L S. Inhomogeneous conduction in the A-V node: A model for re-entry. *Am Heart J* 70:505, 1965.
- Hoffman B I and Cranefield P F. *Electrophysiology of the Heart*. New York, 1960. McGraw-Hill Book Co.
- Langendorf R, Pick A, Edelt A, et al. Experimental demonstration of concealed A-V conduction in the human heart. *Circulation* 32:386, 1965.
- Watanabe Y and Dreifus L S. Electrophysiologic effects of digitalis on A-V transmission. *Am J Physiol* 211:1461, 1966.
- Moore E N, Treston J B and Moe G K. Duration of transmembrane action potential and functional refractory periods of canine feline tendon and ventricular myocardium. *Circ Res* 17:259, 1965.
- Watanabe Y. Purkinje repolarization as a possible cause of the U wave in the electrocardiogram. *Led Proc (Abstr)* 31:313, 1971.
- Watanabe Y and Dreifus L S. Factors determining atrioventricular conduction. (In preparation).
- Watanabe Y and Dreifus L S. Interaction of quinidine and potassium on atrioventricular transmission. *Circ Res* 20:434, 1967.
- Watanabe Y. Effects of electrolytes and antiarrhythmic drugs on atrioventricular conduction. In Sandpe C, Flested Jensen F and Olesen K H, editors. Symposium on cardiac arrhythmias. Södertälje, Sweden, 1970. AB Astra pp 535-557.
- Pires de Carvalho A. Cellular electrophysiology of the atrial specialized tissues. In Pires de Carvalho A, De Mello W C and Hoffman B I, editor. The specialized tissues of the heart. Amsterdam, 1961. Elsevier Publishing Co. pp 115-150.
- Janse M J. Influence of the direction of the atrial wavefront on A-V nodal transmission in isolated hearts of rabbits. *Circ Res* 25:439, 1969.
- Spach M S, Lieberman M, Scott J G, et al.

entered the wall and on the other hand that which has been disposed of by the wall. Comparatively few studies have been aimed to determine the mechanisms and the capacity of the arterial wall to dispose of this accumulation of cholesterol and cholesterol compounds attributes which play a part in preventing excessive lipid accumulation in the arterial wall. Murphy¹ has demonstrated the presence of an equilibrium between free cholesterol of the serum and that of the red blood cells and has shown that the flux of free cholesterol from the cells to the serum increases as the serum cholesterol becomes esterified during incubation. If a similar type of equilibrium exists between free cholesterol of the plasma and that of the arterial tissue then a decrease in cholesterol esterification in plasma might be important in the rate of development of atherosclerosis. This study was undertaken to determine whether such a decrease exists in patients with clinically manifest atherosclerosis of the coronary arteries.

Subjects and methods

Sixty subjects were studied. The first group consisted of 12 patients with acute myocardial infarction documented by a characteristic history, physical examination, electrocardiographic (ECG) features and changes in serum enzymes. There were 11 men and 1 woman ranging in age from 33 to 73 years with a mean age of 57 years. A second group included 16 patients with coronary artery disease in its chronic stages but free of acute myocardial infarction. The diagnosis was confirmed by the characteristic ECG evidence of old myocardial infarction and by the presence of significant arterial obstruction as revealed by coronary cineangiography. There were 15 men and 1 woman ranging in age from 37 to 70 years with a mean age of 56 years. The control group for the present study consisted of 12 men subjects 36 to 65 years old with a mean age of 53 years. Nine of these men have been physicians on the staff at Temple University Health Sciences Center for many years and one of us (LAS) has known them for at least 25 years or more during which time they have been examined periodically for pre insurance physical examinations and occasionally for an annual

physical examination as part of a Temple University service for its alumni. All of these men have been in excellent health over the years and have never had symptoms referable to heart disease. They are extremely active and engage in sports such as sking, handball, squash, swimming, golf and fishing. Physical examination of the cardiovascular system of these subjects has always been normal. Cardiac size by roentgen ray study of the chest and ECGs were always normal and the family history of this group has been remarkably free of any premature atherosclerosis and coronary artery disease. The other three healthy subjects were chosen for the following reasons: two were seen for routine physical examination. Their present and past history was negative for cardiovascular disease. Physical examination and roentgen ray studies of their chests were normal. Their ECGs and two step Master tests were normal and they had family histories of marked longevity. The third subject had been referred because of vague chest distress occurring intermittently for several months. He and his physician desired coronary arteriography to exclude coronary artery disease and this study was normal. A second younger control group composed of 20 young healthy volunteers (medical students, house officers and laboratory technicians) who were free from familial tendency toward premature atherosclerosis was also studied. There were 15 men and five women 25 to 32 years old with a mean age of 27 years.

Blood samples were collected directly into glass tubes with no preservatives added from each of the subjects after an overnight fast. All hemolyzed specimens were discarded. In those patients with acute myocardial infarction specimens were drawn within the first 48 hours after admission into the hospital. Usually two and never more than three subjects were studied in one day and all incubation studies were begun on the day of collection of blood. Studies on healthy subjects and on patients with coronary artery disease were scattered throughout the time of the investigation. All collected blood samples were placed immediately in ice, allowed to clot and transported at once to the laboratory where they were centrifuged immedi-

In vitro serum cholesterol esterification in coronary artery disease

Harold L. Rutenberg, MD*

Alan G. Stern**

Louis A. Soloff MD***

S. deB. Brauerman, MS****

Philadelphia, Pa

Sperry¹ was the first to demonstrate *in vitro* esterification of cholesterol. He reported that incubation of human serum and plasma at 37° C for three days resulted in a marked decrease in free cholesterol with no change in total cholesterol. Le Breton and Pantaléon² demonstrated the participation of serum lecithin in the plasma cholesterol esterification reaction. Glomset and his associates^{3,4} have studied this reaction in detail and recently Glomset⁵ reviewed the literature. In essence during incubation of plasma cholesterol esters are formed in the plasma by the action of lecithin cholesterol acyltransferase (LCAT) which appears to react preferentially with high density lipoproteins to catalyze the transfer of fatty acids from the 2 position of lecithin to the hydroxyl group of free cholesterol. The esterified cholesterol is subsequently transferred in

part to the very low density lipoproteins.⁶ On the other hand Schumaker and Adams⁷ have suggested the possibility that the primary function of LCAT is related to maintenance of lipoprotein structure. They have proposed that as triglyceride is removed from the lipoprotein by the action of lipoprotein lipase LCAT causes a concomitant reduction in the lipoprotein surface by the removal of 1:1 units of lecithin and free cholesterol thus enabling the lipoproteins to retain spherical shape and similar surface properties. Although other cholesterol esterifying systems may be present in plasma, *in vitro* cholesterol esterification has been used as one measure of LCAT activity.⁸

The arterial wall contains variable amounts of cholesterol, cholesterol esters, and phospholipids; the total amount representing a balance between on the one hand that which has been synthesized or has

From the Division of Cardiology, Department of Medicine and the Department of Biometrics, Temple University Health Sciences Center, Philadelphia, Pa.

Supported in part by United States Public Health Training Grant HE057125 and by the Council for Tobacco Research, U.S.A.

Received for publication November 15, 1971.

Reprint requests to Louis A. Soloff, MD, Chief, Division of Cardiology, Temple University Health Sciences Center, 3401 North Broad St., Philadelphia, Pa. 19140.

*Assistant Professor of Medicine, Temple University Department of Medicine.

**Senior Medical Student, Temple University.

***Professor of Medicine and Chief, Division of Cardiology, Temple University Department of Medicine.

****Assistant Professor of Biometrics, Temple University Department of Medicine.

Presented at the International Symposium on Atherosclerosis, University of Toronto, Toronto, Ontario, Canada, June 12, 1971.

Table II Triglyceride and cholesterol concentration in mg per 100 ml—data for 12 age matched controls

Age matched controls	Age	Sex	Triglycerides	TC	FC†	FC† after incubation (hrs)			
						3	6	24	48
M N	49	M	44	207	51	46	40	20	24
M R	53	M	710	210	47	46	40	23	21
H B	52	M	194	211	67	55	47	30	23
G B	65	M	215	212	67	53	44	29	21
J H	52	M	64	220	54	47	43	33	27
H K.	50	M	159	220	56	45	37	24	18
A P	61	M	157	256	74	67	60	41	32
W L	49	M	347	260	78	68	56	35	26
L S	65	M	87	282	86	72	60	55	35
J G	64	M	54	297	69	62	61	44	39
H S	56	M	53	310	83	73	67	49	49
J K.	36	M	173	320	92	82	55	43	41

† TC = total cholesterol
FC = free cholesterol

with the Michael Reese value with 99 per cent accuracy. The normal range given by that laboratory was 30 to 110 mg per cent at the time this study was done but its normal range has since been established at 30 to 135 mg per cent.

The clinical status of each of the patients with acute myocardial infarction is included and it should be noted that although many had transient arrhythmias and three had mild to moderate congestive heart failure none had any signs of shock or pulmonary edema within the first 48 hours of admission, the time period in which blood was drawn for these studies. Three of the patients ultimately had stormy hospital courses but all were eventually discharged from the hospital.

Results

Tables I to IV show the changes in serum free cholesterol after incubation at 37°C for 3, 6, 24 and 48 hours for all subjects in the study. Table V reveals the mean data for each of the four groups studied with comparisons between the groups for total and free cholesterol and cholesterol esterification at 3, 6, 24 and 48 hours. It should be noted that both total and free cholesterol concentrations were significantly lower in the young controls, a finding which makes

comparisons of esterification somewhat difficult. In addition, although not significantly different, the mean total cholesterol concentrations in subjects with acute myocardial infarction was 15 mg per 100 ml higher than that of the age matched healthy controls. Nevertheless, the serum free cholesterol concentration prior to any incubation was significantly higher in those subjects with acute myocardial infarction compared to the age matched healthy controls ($p < 0.05$). The comparison of subjects with chronic coronary artery disease with the age matched controls where both total and free cholesterol concentrations were similar, revealed significantly decreased esterification ($p < 0.05$) after 6, 24 and 48 hours incubation.

The data were then analyzed from another perspective. This was considered because of reports in the literature suggesting a tendency for *in vitro* cholesterol esterification to be higher at hypercholesterolemic concentration.^{11,12} There were nine subjects in the study with total serum cholesterol concentrations > 300 mg per 100 ml. Four of these presented with chronic coronary artery disease, three with acute myocardial infarction and two were age matched controls. This group of subjects was separated and the average slope which

Table I Triglyceride and cholesterol concentration in mg per 100 ml—data for 20 young control subjects

Young controls	Age	Sex	Triglycerides	TC*	FC†	FC† after incubation (hrs)			
						3	6	24	48
F C	25	M	59	161	47	43	41	25	70
S I	26	F	23	171	60	56	48	32	79
J B	24	M	47	172	43	38	30	18	14
S M	29	M	25	176	39	32	30	18	17
W H	25	M	74	190	57	45	40	22	20
I S	25	F	56	196	55	54	43	24	18
W J	30	M	47	197	46	40	34	23	18
N B	24	M	47	198	62	56	58	35	35
J A	28	F	39	209	62	54	47	35	31
I M	30	M	50	209	61	56	55	40	36
R T	24	M	110	211	66	58	53	39	36
H N	30	M	38	223	67	54	47	31	29
B H	27	M	70	226	48	40	31	15	13
J P	32	M	168	232	77	71	43	32	24
P W	24	M	72	233	58	50	47	28	24
F V	30	M	118	251	64	54	46	34	29
A K	26	M	62	252	55	52	52	37	28
M N	23	M	22	256	83	78	70	15	47
C K	24	M	90	260	78	70	58	47	43
I B	32	F	72	261	69	51	44	25	73

*TC = total cholesterol

†FC = free cholesterol

ately at 3,000 X g for 15 minutes at 4° C and the serum was divided into two aliquots. Lipid extraction (acetone ethanol V/V mixture) was immediately added to the first of these aliquots which was to serve as the pre incubation control. The second serum aliquot was placed in a 15 ml disposable sterile test tube and the tube incubated in a water bath at 37° C. Two ml samples of serum were removed by sterile pipettes after 3, 6, 24 and 48 hours of incubation and 0.5 ml of the serum samples immediately pipetted into the extraction mixture. All determinations were done in triplicate. Serum total and free cholesterol concentrations were determined on all of the samples using the method of Zak and associates.⁹ Since the total cholesterol at all incubation times remained relatively constant within the 1 to 2 per cent variation in this method the decreases in free cholesterol concentrations observed after the various incubations were used as a measure of cholesterol esterification and expressed as mg of free cholesterol ester

fied per 100 ml of serum. All chemical determinations were performed in the Research Lipid Laboratory and all samples were handled by the same two research technicians who would work simultaneously on each sample (if two subjects were studied) so that there could be no difference in incubation times. If three subjects were studied on one day addition of the extraction mixture to the third sample was prolonged at most by one minute. All samples for each of the incubation times were then stored at 4° C and kept until the final incubation time so that all of the samples for a particular subject would be analyzed at the same time.

Serum triglycerides were analyzed by a slight modification of the method described by Carlson¹⁰ as performed by the Lipid Standardization Laboratory of the Communicable Disease Center in Atlanta. Georgia. Standards were supplied by the Michael Reese Research Foundation in Chicago and determination of triglycerides in these standards by our technique correlated

Table IV Triglyceride and cholesterol concentration in mg per 100 ml—data for 16 subjects with chronic coronary artery disease

Chronic CAD†	Age	Sex	Triglycerides	TC	FC†	FC† after incubation (hrs)			
						3	6	24	48
E. F.	50	M	113	195	59	50	44	36	29
H. H.	56	M	—	198	61	54	52	40	32
L. H.	46	M	—	201	67	63	58	41	35
M. G.	62	M	—	214	66	54	51	46	39
G. M.	70	M	93	218	61	56	55	40	36
A. L.	69	M	59	220	70	65	59	42	41
A. M.	37	M	48	229	62	59	59	57	46
W. S.	56	M	52	242	84	79	73	60	56
H. S.	51	M	59	247	61	56	54	50	40
J. H.	54	M	152	253	72	62	58	44	37
S. H.	53	M	70	253	65	57	57	38	32
H. W.	57	M	—	278	86	80	74	66	65
M. M.	49	M	106	312	96	81	77	60	54
J. B.	57	M	62	322	93	83	77	58	51
L. B.	53	M	212	322	83	70	65	47	38
M. F.	58	M	127	340	111	96	90	70	66

TC = total cholesterol

FC = free cholesterol

CAD = coronary artery disease

matched healthy controls slightly above those subjects with coronary artery disease. The mean esterification was significantly decreased at six hours in those subjects with acute and chronic coronary artery disease when compared to age matched healthy controls. This decrease in esterification in subjects with coronary artery disease was even more significant ($p < 0.01$) at 48 hours compared to the age matched healthy controls. At 24 hours there was a significant decrease in the esterification of only those subjects with chronic coronary artery disease compared to the age matched healthy controls. There were no significant differences in esterification between all groups at 3 hours although the differences were in the direction of those noted to be significant at subsequent times.

There were no significant differences in esterification between the younger controls and the older age matched healthy control group although the mean absolute values for esterification were always higher in the older normal individuals. The mean free cholesterol concentration prior to incubation was highest in subjects with acute myocardial infarction. This value differed

significantly ($p < 0.05$) from the mean value of the young controls but did not differ significantly from the mean value for the age matched healthy controls despite the lower absolute mean free cholesterol concentration in the latter group.

It was noted that the trend of the average free cholesterol appeared to be linear with log time from 3 to 48 hours. Since the values for each individual over time were correlated it was not possible to use the standard regression method to analyze the differences among the slopes for the three groups. However it was possible to compute a slope for each individual within each group and then use an analysis of variance technique^{13,14} on the computed slopes to assess statistical differences among the average slopes. The pooled within group variation of the slopes was used as the estimate of error. This method is equivalent to testing if the average linear trend differed among the groups. Fig. 2 shows a comparison of these average slopes for the four groups with the mean total cholesterol concentrations held constant as indicated above. The slopes of both the acute and chronic coronary artery disease subjects

Table III Triglyceride and cholesterol concentration in mg per 100 ml—data for 12 subjects with acute myocardial infarction

Acute myocardial infarction	Age	Sex	Triglycerides	TC*	FC†	FC† after incubation (hrs)				Clinical status
						3	6	24	48	
L F	35	M		194	64	55	47	33	24	Uncomplicated course
M C	54	M	145	201	62	53	52	30	28	Frequent PVC† and PAC Otherwise uncomplicated course
G E	72	M	100	211	79	75	65	51	55	Sinus bradycardia with escape AV junctional rhythm occas PVC mild CHF 1st and 2nd day
M K	64	M	54	225	68	60	64	62	48	Sinus bradycardia shifting atrial and A V junctional pacemaker
L L	73	M	55	226	68	57	59	44	41	Transient short episodes of atrial flutter and fibrillation
A R	70	M	72	228	61	61	64	—	52	1st degree heart block and freq PVC occurs in sequence for first 2 days. Two episodes of recurrent chest pain with vent tachycardia on 6th hospital day
B S	45	M	191	236	76	62	53	48	44	Pericardial friction rub 2nd day Post myocardial infarction syndrome 25th day
L W	67	M	140	265	87	79	77	65	55	Moderate emphysema Uncomplicated course
I P	37	M	110	275	82	75	70	48	53	Recurrent short episodes of supra ventricular tachycardia
R H	61	M	293	370	109	93	85	57	51	Occas PVC ventricular fibrillation 13th day resuscitated
M E	63	F	57	370	111	105	103	73	66	Sinus tachycardia CHF pericardial friction rub 7th day Multiple recurrent episodes ventricular tachycardia 18th to 3rd day
R S	47	M	98	374	116	99	90	74	67	Frequent PVC mild CHF

*TC = total cholesterol †FC = free cholesterol

†Abbreviations PVC = premature ventricular contraction PAC = premature atrial contraction AV = atrioventricular CHF = congestive heart failure

characterized the changes in free cholesterol over the various incubation times with the latter expressed logarithmically was compared to a slope characterizing the changes in free cholesterol for all of the other subjects (> 300 mg per 100 ml) (Fig 1). This comparison suggested a rather marked increase in esterification in this group with total cholesterol concentrations > 300 mg per 100 ml despite the fact that both diseased and normal subjects were included. It was thus postulated that the groups with chronic coronary artery disease and acute myocardial infarction and to a lesser extent, the age matched healthy controls might have had mean esterifications which were overly weighted

by the presence of these several subjects whose cholesterol concentrations were > 300 mg per 100 ml.

For this reason and because it was felt that a meaningful comparison could be made only if the mean total cholesterol concentration could be held more firmly constant in the four groups, those subjects with total cholesterol concentrations > 300 mg per 100 ml and those with total cholesterol concentrations < 195 mg per 100 ml were removed from the following analysis. Note that this resulted in the mean total cholesterol concentrations being held relatively constant (Table VI), the mean level in the young healthy controls being slightly below, and the mean level in the older age

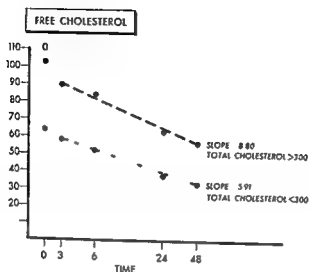


Fig 1 Comparison of the slopes describing the decrease in free cholesterol after incubation of serum for 3, 6, 24 and 48 hours at 37°C of nine subjects with total serum cholesterol > 300 mg per 100 ml and 37 subjects with total serum cholesterol < 300 mg per 100 ml. The abscissa (time) is expressed logarithmically. 0 refers to mean preincubation control values.

revealed significantly decreased esterification at the $p < 0.01$ level of significance when compared to those age matched healthy controls. Note also the similarity in the slopes of the young healthy and age matched healthy subjects.

Discussion

Our findings indicate that *in vitro* esterification of plasma cholesterol does not change with age in the healthy adult and that it is diminished in patients with coronary artery disease compared to healthy subjects. This latter finding confirms and extends that of Berlin, Oldfelt and Vikrot.¹⁵ However, these studies do not pinpoint the mechanism responsible for this difference nor do they indicate that this *in vitro* finding has a physiologic counterpart *in vivo*. This is so because of the substrates necessary for cholesterol esterification, only the cholesterol concentration was controlled and the possible presence of inhibitors and activators of the enzymatic reaction could not be detected in addition to the fact that the technique itself might not represent a physiologic reaction.

The importance of controlling the level of blood cholesterol is evident from our studies that show that *in vitro* esterification of

plasma cholesterol is related to the amount of cholesterol in the blood. This has been found by some^{11, 12} and denied by others.^{14, 17} Part of the confusion in the literature may be due to the use of different species differences in measuring esterification and the failure to separate healthy subjects from those with coronary artery disease. On the other hand, we did not measure the quantity of lecithin in the blood or perform quantitative measurements of lipoproteins of the subjects in the study. We could detect no significant differences in lipoprotein patterns as determined by paper¹⁸ and by cellulose acetate¹⁹ electrophoresis in all of the age matched cholesterol matched subjects nor could we find quantitative differences using densitometric methods of comparison. However, this latter method is regarded by our statistical department as meaningless because of the variable overlapping of the curves representing individual lipoproteins. None of these methods is an adequate substitute for quantitation of all substrates that are essential for esterification and determining the rate of cholesterol esterification. Thus, Nichols and Long²⁰ and Ho and Nichols²¹ using sonicated dispersions of mixtures of cholesterol and lecithin as substrates for the assay of

Table VA Decrease in free cholesterol (cholesterol esterification) after incubation of serum for 3, 6, 24, and 48 hours at 37° C

Variables	Young controls	Age matched controls	Acute infarction	Chronic CAD
Number	20	12	12	16
Mean age (range)	27.2 (23-35)	54.6 (36-65)	57.3 (45-73)	56.1 (31-70)
Total cholesterol†	214.2 ± 31.77*	249.5 ± 42.74	264.6 ± 68.4	257.8 ± 48.2
Free cholesterol†	59.9 ± 11.78	69.2 ± 14.0	81.9 ± 19.9	74.8 ± 15.5
Cholesterol esterification‡				
3 hours	7.8 ± 3.7	9.5 ± 3.6	9.1 ± 4.9	8.3 ± 3.91
6 hours	13.5 ± 7.9	18.3 ± 8.3	12.8 ± 8.6	12.1 ± 5.0
24 hours	28.2 ± 8.5	33.7 ± 8.0	28.7 ± 13.2	25.1 ± 9.3
48 hours	33.2 ± 7.3	39.5 ± 9.5	33.3 ± 13.3	31.3 ± 8.8

*Values given are mean ± standard deviation

†Cholesterol concentrations expressed in mg per 100 ml

Table VB Outcome of comparison of parameters of four groups

Variables	Young controls 15			Age matched controls 15		Acute vs Chronic
	Age matched	Acute	Chronic	Acute	Chronic	
Total cholesterol	p < 0.05	p < 0.01	p < 0.05	NS*	NS	NS
Free cholesterol	NS	p < 0.001	p < 0.02	p < 0.05	NS	NS
Cholesterol esterification						
3 hours	NS	NS	NS	NS	NS	NS
6 hours	NS	NS	NS	NS	p < 0.05	NS
24 hours	NS	NS	NS	NS	p < 0.05	NS
48 hours	NS	NS	NS	NS	p < 0.05	NS

*Values not statistically significant

Table VI Decrease in free cholesterol (cholesterol esterification) after incubation of serum for 3, 6, 24, and 48 hours at 37° C

Variables	Young controls*	Age matched controls	Acute infarction	Chronic CAD
Number	15	10	9	12
Mean age (range)	27.3 (23-32)	56.3 (49-65)	57.4 (35-73)	56.8 (37-70)
Total cholesterol†	227.6 ± 23.9	236.5 ± 32.9	229.0 ± 27.0	229.0 ± 25.9
Free cholesterol	63.4 ± 10.53	65.5 ± 12.0	71.9 ± 9.4‡	67.8 ± 8.9
Cholesterol esterification‡				
3 hours	8.2 ± 3.8	9.0 ± 3.9	7.8 ± 4.0	6.6 ± 2.7
6 hours	14.1 ± 8.8	16.7 ± 6.5	10.7 ± 7.4§	10.0 ± 3.4
24 hours	28.7 ± 9.4	32.1 ± 7.0	25.6 ± 8.9	21.2 ± 7.3¶
48 hours	34.5 ± 7.4	38.9 ± 9.6	27.4 ± 9.0¶	27.2 ± 5.6¶

*Mean total cholesterol concentration held relatively constant for all groups

†All cholesterol concentrations expressed in mg per 100 ml

‡Values given are means ± standard deviation

§Significantly different from age matched normals at p < 0.05

||Significantly different from the age matched normals at p < 0.02

¶Significantly different from the age matched normals at p < 0.01

¶Significantly different from the young normals at p < 0.05

For all these reasons our *in vitro* findings cannot as yet be interpreted as indicating that patients with coronary artery disease have a decrease in LCAT activity. We have however recently demonstrated by incubation of inverted human iliac arterial segments with intima exposed to human serum in which the cholesterol esterifying activity was present and in human serum in which the enzyme has been inactivated by heating to 56°C for 30 minutes that the enzyme must be present for free cholesterol to leave the arterial wall and enter the serum.¹⁰ We therefore believe it is important that efforts be made to purify LCAT and to develop methods for measuring accurately its initial rate of activity.

Summary

The mean serum *in vitro* cholesterol esterification as determined by the decrease in the concentration of free cholesterol after incubation of serum for 3, 6, 24, and 48 hours has been compared in four groups: subjects with acute myocardial infarction, subjects with chronic coronary artery disease, age matched healthy controls, and young healthy controls.

The original data revealed a significantly decreased esterification in subjects with chronic coronary artery disease compared to the group of age matched controls ($p < 0.05$) and a significantly increased free cholesterol in subjects with acute myocardial infarction compared to the age matched healthy subjects ($p < 0.05$).

Comparisons of these four groups were then made by removal of those subjects with total cholesterol > 300 mg per 100 ml and < 190 mg per 100 ml because it was felt that a meaningful comparison could be made only if the mean total cholesterol concentration could be held constant for each group. This was also done to avoid the possibility that since cholesterol esterification tends to be higher in subjects with hypercholesterolemia, those groups with coronary artery disease might show mean esterifications that were overly affected by the presence of more subjects with total cholesterol > 300 mg per 100 ml. When the statistical analysis was performed the mean *in vitro* cholesterol esterification was significantly decreased at 6 hours ($p < 0.01$), 24 hours, and 48 hours

($p < 0.01$) in subjects with chronic coronary artery disease compared to age matched controls and was significantly decreased at 6 hours ($p < 0.05$) and 48 hours ($p < 0.01$) in subjects with acute myocardial infarction compared to the age matched controls. The average slope describing cholesterol esterification over time was significantly decreased in acute myocardial infarction and chronic coronary artery disease ($p < 0.01$). On the other hand there were no significant differences between the young healthy group and the older age matched healthy subjects.

Although these findings suggest the possibility that subjects with coronary artery disease have a deficiency of lecithin cholesterol acyltransferase, the limitations of this study are stressed. It is unlikely that a firm conclusion will be available until an accurate method of determining the initial rate of plasma cholesterol esterification is available and until the enzyme is purified.

We thank Fay Baldwin and Peggy Nickel for their technical assistance and Elizabeth Wolf for her aid in preparation of the manuscript.

REFERENCES

1. Sperry W M. Cholesterol esterase in blood. *J Biol Chem* 111:467 1935.
2. Le Breton E and Pantaleon J. Cholestero-ferase et lecithase du plasma sanguin. Leur action couplée. *Arch Sci Physiol* 1:199 1947.
3. Glomset J A, Parker F T, Jaden M and Williams R H. The esterification *in vitro* of free cholesterol in human and rat plasma. *Biochim Biophys Acta* 38:398 1962.
4. Glomset J A. The mechanism of the plasma cholesterol esterification reaction. Plasma fatty acid transferase. *Biochim Biophys Acta* 63:128 1962.
5. Glomset J A. The plasma lecithin cholesterol acyltransferase reaction. *J Lipid Res* 9:155 1968.
6. Akanuma Y and Glomset J. *In vitro* incorporation of cholesterol- C^{14} into very low density lipoprotein cholesterol esters. *J Lipid Res* 9:611 1968.
7. Schumaker V N and Adams G H. Circulating lipoproteins. *Ann Rev Biochem* 38:113 1969.
8. Murray J R. Erythrocyte metabolism. III. Relationship of energy metabolism and serum factors to the osmotic fragility following incubation. *J Lab Clin Med* 60:86 1962.
9. Zak B, Dickenson R C, White E G, Burnett H and Cherney J J. Rapid estimation of free and total cholesterol. *Am J Clin Pathol* 24:1307 1954.

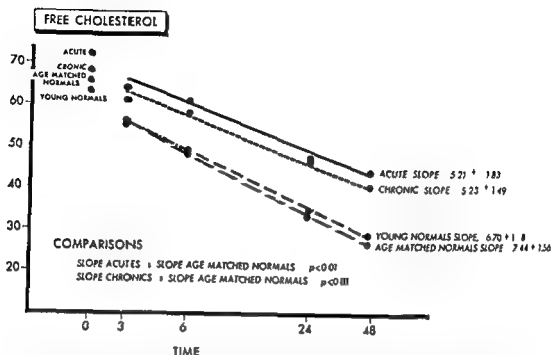


Fig 2 Comparison of the slopes describing the decrease in free cholesterol after incubation of serum for 3 6 24 and 48 hours at 37° C in subjects with chronic coronary artery disease acute myocardial infarction age matched controls and a younger control group mean cholesterol concentration held constant for all groups. The abscissa (time) is expressed logarithmically 0 refers to mean preincubation control value

cholesterol esterification found that the rate of enzyme activity might be partly inhibited with increased concentrations of lecithin or with increasing molar proportions of free cholesterol. They postulated that differences in reactivity of the different classes of serum lipoproteins with LCAT may result from differences in the relative proportions of unesterified cholesterol and lecithin on the lipoprotein surface accessible to the enzyme.

Furthermore, because the enzyme responsible for esterification has not been purified, the possibility of the presence of inhibitors and activators of the enzyme rather than a decrease in the LCAT enzyme cannot be excluded as one mechanism responsible for differences in cholesterol esterification. Gherondache² has demonstrated inhibition of cholesterol esterification during and after infusion of catecholamines. Endogenous catecholamines or elevation of serum free fatty acids which are known to occur with acute myocardial infarction might be one mechanism that explains our initial free cholesterol findings in the group with acute myocardial infarction.

Finally, our *in vitro* findings may have no physiologic counterpart *in vivo*. *In vivo*

effects of physical forces total blood content including its cells,⁸ arterial wall^{22,23} and particularly the arterial wall LCAT activity,^{26,27} were all omitted from our *in vitro* studies. Perhaps most important is our observation that differences in the esterification between the groups at the initial, 3 hour incubation just fell short of statistical significance. This could be due to the small numbers of subjects and to the large individual variations.

It is generally agreed that it is most important to obtain as accurate data as possible on the initial rate of esterification. It is for this reason that another method of measuring cholesterol esterification has been introduced. This method consists of incubating small amounts of plasma for one to six hours at 37° C with a substrate composed of heat inactivated plasma and radioactively labeled free cholesterol added as an albumin stabilized emulsion or coated onto Celite particles with measurement of the formation of labeled cholesterol esters. However, this method has the disadvantage of using exogenous substrates that can produce spurious results. Since our study was completed Stolke and Norum⁸ have developed and reported a method that may circumvent this objection.

Effect of glucagon on automaticity, threshold for stimulation, and atrioventricular conduction in patients with impaired impulse formation or conduction

Akira Nishimura MD

R B Forner MD

John F Williams Jr MD

Galveston Texas

The positive inotropic and chronotropic effects of glucagon have been amply demonstrated in both experimental animals¹ and man.^{2,3} The former action encouraged the drug's clinical use and a significant number of patients with heart failure have now received this agent therapeutically. Although glucagon's effectiveness appears to vary markedly,^{4,5} it has been a uniform observation that the hormone is remarkably free of major side effects most noticeable has been the lack of arrhythmias. However in the experimental animal glucagon has been found to exert significant electrophysiologic effects. The hormone has been reported to enhance atrioventricular (A V) conduction⁶ and to reverse the depression of A V conduction produced by propranolol.⁷ In addition glucagon accelerates nodal pacemakers⁸ whereas ventricular automaticity may be unaffected⁹ or increased.^{10,11}

At present no systematic investigation of the electrophysiologic effects of glucagon in patients with disorders of impulse formation or conduction has been reported and

it is unclear as to whether this agent may produce effects similar to those described in animals. In view of the clinical importance of such information the following study was undertaken.

Methods

The effect of glucagon on A V conduction was determined in 11 patients with atrial fibrillation or first or second-degree heart block. In the four patients with atrial fibrillation in each of whom the ventricular response had been adequately controlled pharmacologically changes in the ventricular rate were used to reflect changes in A V conduction. Of the three patients with second-degree heart block two had a fixed 2:1 ventricular response with normal QRS complexes whereas the other had a Mobitz type II block with a varying ventricular response. The relationship of atrial to ventricular depolarization was used to measure A V conduction in the patients with heart block.

The effect of glucagon on automaticity was assessed in nine patients with ectopic

From the Cardiology Division, Department of Medicine, University of Texas Medical Branch at Galveston, Texas. Supported in part by U.S. Armed Forces Public Health Service Training Grant No. HL 13639 from the National Heart, Lung, and Blood Institute. Received for publication April 19, 1971. Reprint requests to Dr. John F. Williams, Jr., MD, Department of Medicine, University of Texas Medical Branch at Galveston, Box 377550.

- 10 Carlson L A Determination of serum triglycerides *J Atheroscler Res* 3:334 1963
- 11 Monger L A and Nestel P J Relationship between the concentration and the rate of esterification of free cholesterol by the plasma esterification system *Clin Chim Acta* 15:269 1967
- 12 Wells I C and Rongone E I Dietary cholesterol and serum cholesterol esterifying activity in rabbits *Proc Soc Exp Biol Med* 130:661 1969
- 13 Winer B J Statistical principles in experimental design New York 1962 McGraw Hill Book Co chapters 4 and 7
- 14 Danford M B Hughes H M and McNee R C On the analysis of repeated measurements experiments *Biometrics* 16:547 1960
- 15 Berlin R Oldfelt C O and Vikrot O Acute myocardial infarction and plasma phospholipid levels *Acta Med Scand* 185:139 1969
- 16 Shapiro I I Jastremsky J A and Kritechevsky D Effect of hypercholesteremia on the activity of serum lecithin cholesterol acyltransferase *Lipids* 3:381 1968
- 17 Rose H G Serum lecithin cholesterol acyltransferase in cholesterol fed rabbits *Circulation* 42 (Suppl III) 3 1970
- 18 Lees R S and Hatch I T Sharper separation of lipoprotein species by paper electrophoresis in albumin containing buffer *J Lab Clin Med* 61:518 1963
- 19 Chin H P and Blakenhorn D H Separation and quantitative analysis of serum lipoproteins by means of electrophoresis on cellulose acetate *Clin Chim Acta* 20:305 1968
- 20 Nichols A V and Gong I L Use of sonicated dispersions of mixtures of cholesterol with lecithin as substrates for lecithin cholesterol acyltransferase *Biochim Biophys Acta* 231:175 1971
- 21 Ho W K K and Nichols A V Interaction of lecithin cholesterol acyltransferase with sonicated dispersions of lecithin *Biochim Biophys Acta* 231:185 1971
- 22 Gherondache C N Physiologic variations in the cholesterol esterifying activity of serum *J Clin Endocrinol Metab* 23:1024 1963
- 23 Day A J and Tume R K In vitro incorporation of ¹⁴C labelled oleic acid into combined lipid by foam cells isolated from rabbit atherosclerotic lesions *J Atheroscler Res* 9:141 1969
- 24 Newman H A I and Zilvermut D B Uptake and release of cholesterol by rabbit atherosclerotic lesions *Circ Res* 18:793 1966
- 25 Dayton S and Hashimoto S Movement of labeled cholesterol between plasma lipoprotein and normal arterial wall across the intimal surface *Circ Res* 19:1041 1966
- 26 Abdulla Y H Orton C C and Adams C W M Cholesterol esterification by transacylation in human and experimental atherosclerotic lesions *J Atheroscler Res* 8:967 1968
- 27 Abdulla Y H Adams C W M and Bayliss O B The location of lecithin cholesterol transferase activity in the atherosclerotic arterial wall *J Atheroscler Res* 10:729 1969
- 28 Stokke K T and Norum K R Determination of lecithin cholesterol acyltransferase in human blood plasma *Scand J Clin Lab Invest* 27:21 1971
- 29 Rutenberg H L and Soloff L A A possible mechanism of egress of free cholesterol from the arterial wall *Nature* 230:171 1971

Table I Clinical data

Patient	Age	Diagnosis	Rhythm	Heart failure
V. J.	43	CAHD HCVD	AF	+
L. H.	40	RIID	AF	+
L. B.	86	HDUE	AF	+
E. T.	57	Post aortic valve replacement	AF	+
M. B.	49	Myotonia dystrophica	1 HB	-
A. C.	50	HCVD	1 HB	+
J. L.	61	HDUE	1 HB	-
C. P.	43	COPD	1 HB	+
W. E.	70	HDUE	2 HB	-
W. P.	74	HDUE	2 HB	-
E. C.	64	HDUE	2 HB	-
M. R.	27	Congenital heart block	3 HB†	-
R. M.	29	Congenital heart block	3 HB†	-
R. C.	60	CAHD	3 HB†	+
M. G.	49	CAHD	3 HB†	+
E. L.	73	CAHD	3 HB	-
G. T.	68	CAHD	3 HB	-
M. O.	45	CAHD	3 HB	-
C. F.	5	CAHD—digitals intoxication	Nodal tachycardia	-
V. S.	37	Amyloidosis	Sinus arrest nodal rhythm	-

CAHD Coronary atherosclerotic heart disease
 HCVD Hypertensive cardiac disease
 RIID Rheumatic heart disease
 HDUE Heart disease of undetermined type
 COPD Chronic obstructive pulmonary disease
 HB Heart block (1 normal QRS complex)
 AF Atrial fibrillation
 † Present

pacemaker in the three patients with complete heart block and wide QRS complexes. Whether these latter patients had pacemakers distal to the bifurcation of the bundle or bundle branch block with the pacemaker proximal to the bifurcation was not determined. However the latter mechanism is suggested in patient M. O. whose control rate was generally faster than that expected with an idioventricular pacemaker. In the patient with sinus arrest and a nodal escape mechanism a slight increase in the rate of this pacemaker was observed after glucagon. Since the cardiac effects of injections of glucagon generally appear and dissipate fairly rapidly ** the increase in rate which occurred relatively late and persisted throughout the remainder of the study in this patient may represent spontaneous variation and not glucagon effect. In the patient with digitals induced nodal

tachycardia a maximum increase of only 6 beats per minute was observed.

Six of the 20 patients had ventricular premature contractions during the control period. No significant change in the frequency of the premature contractions was noted during the study.

The effect of glucagon on the threshold for ventricular stimulation is presented in Table IV. In all patients stimulation threshold had been reproducible on multiple determinations before glucagon. In only one of the nine patients was a significant change in stimulation threshold observed after glucagon. In this patient threshold increased by 60 per cent at the 3 minute period but returned to control by 10 minutes.

No significant change in systemic arterial pressure was observed after glucagon. The only side effects noted with glucagon were

pacemakers by determining the drug's effect on the rate of this pacemaker. Seven patients had complete heart block, four with QRS complexes of normal duration. Two patients had nodal pacemakers with apparently normal A-V conduction. One of these latter patients had a digitalis-induced nodal tachycardia, whereas the other had persistent sinoatrial asystole but could be paced from the atrium up to a rate of 140 per minute with no evidence of impaired A-V conduction. In patients with intracardiac pacemakers the spontaneous rate was determined during cessation of pacing and only those patients who could tolerate this without developing symptoms were selected for study.

The effect of glucagon on threshold for stimulation was determined in nine patients with temporary transvenous pacemakers. A Cordis Synchrocorder II which permits stepwise changes in current flow of 0.1 ma was used as the external power source. The minimal milliamperage necessary for stimulation was determined on several occasions and thereafter was maintained at the lowest setting which permitted constant pacing. Pacing rate ranged from 70 to 80 beats per minute. After glucagon administration the minimal milliamperage necessary for stimulation was again determined at each of the periods designated below. The stimulation threshold was determined from the settings on the power supply and therefore was not necessarily that delivered to the endocardium.

Six patients were receiving a digitalis glycoside but in only one was this substantiated as being a causative or contributing factor to the arrhythmia. No patient had suffered a myocardial infarction within the preceding six weeks and with the exception of the patient with nodal tachycardia the existing cardiac rhythm had been stable for at least seven days preceding the study.

Indirect or direct brachial arterial pressure and standard Lead II of the electrocardiogram (ECG) were recorded in all patients. Furthermore, in two patients with first degree heart block atrial, ventricular and His bundle potentials were recorded with intracardiac electrodes utilizing the technique described by Damato and associates.¹³

In all patients an infusion of 5 per cent glucose in water was begun and after control measurements were obtained 5 mg of glucagon dissolved in normal saline was given intravenously over 30 seconds. Measurements of blood pressure, 30 second recordings of the standard ECG, and when appropriate, stimulation threshold were obtained 1, 3, 5, 10, 15, and 30 minutes after completion of the injection. In the patients with first degree heart block brief recordings at a paper speed of 100 mm per second were also obtained at these time periods.

Results

The clinical data for each individual are given in Table I.

The individual results of the effect of glucagon on A-V conduction are presented in Table II. No clinically significant change in ventricular rate occurred in patients with atrial fibrillation following glucagon injection. One of these patients (E.T.) required propranolol (80 mg per day) as well as digoxin to control his ventricular response before glucagon. In the four patients with first degree heart block the P-R interval increased by only 10 msec in one was unchanged in another, and decreased by a maximum of 15 msec in the remaining two. In the latter two patients recordings from intracardiac electrodes revealed that the decrease in P-R interval which was maximum at the 1 minute period and thereafter returned toward control, resulted from a decrease in the P-His bundle interval with an unchanged H-Q interval. In none of the patients with second degree block was there a significant change in conduction following glucagon administration. Although not included in Table II, glucagon did not restore A-V conduction in any patient with complete heart block.

The effect of glucagon on automaticity is presented in Table III. In three of the four patients with complete heart block and pacemakers above the bifurcation of the bundles no change in the rate of the dominant pacemaker was observed after glucagon. In the remaining patient the rate increased by a maximum of 10 beats per minute at the 1 minute period and thereafter returned toward control values. Glucagon did not alter the rate of the dominant

Table 1 Clinical data

Patient	Age	Diagnosis	Rhythm	Heart failure
V J	43	CAHD HCVD*	AF	+
L H	40	RHD	AF	+
L B	86	HDUE	AF	+
E T	57	Post aortic valve replacement	AF	+
M B	49	Myotonia dystrophica	1 HB	-
A C	50	HCVD	1 HB	+
J L	61	HDUE	1 HB	-
C P	73	COPD	1 HB	+
W E	70	HDUE	2 HB	-
W P	74	HDUE	2 HB	-
E C	64	HDUE	2 HB	-
M R	27	Congenital heart block	3 HB†	-
R. M.	29	Congenital heart block	3 HB†	-
R C	60	CAHD	3 HB†	+
M G	79	CAHD	3 HB†	+
E R	73	CAHD	3 HB	-
G T	68	CAHD	3 HB	-
M O	75	CAHD	3 HB	-
C F	75	CAHD—digitalis intoxication	Nodal tachy cardia	-
V S	37	Amyloidosis	Sinus arrest nodal rhythm	-

CAHD Coronary thrombosis of heart disease
 HCVD Hypertensive cardiac disease
 RHD Rheumatic heart disease
 HDUE Heart disease of undetermined etiology
 COPD Chronic obstructive pulmonary disease
 BB Heart block (1 normal QRS duration)
 AF Atrial fibrillation
 † Prem L

pacemaker in the three patients with complete heart block and wide QRS complexes. Whether these latter patients had pacemakers distal to the bifurcation of the bundle or bundle branch block with the pacemaker proximal to the bifurcation was not determined. However the latter mechanism is suggested in patient M O whose control rate was generally faster than that expected with an idioventricular pacemaker. In the patient with sinus arrest and a nodal escape mechanism a slight increase in the rate of this pacemaker was observed after glucagon. Since the cardiac effects of injections of glucagon generally appear and dissipate fairly rapidly ** the increase in rate which occurred relatively late and persisted throughout the remainder of the study in this patient may represent spontaneous variation and not glucagon effect. In the patient with digitalis-induced nodal

tachycardia a maximum increase of only 6 beats per minute was observed.

Six of the 20 patients had ventricular premature contractions during the control period. No significant change in the frequency of the premature contractions was noted during the study.

The effect of glucagon on the threshold for ventricular stimulation is presented in Table IV. In all patients stimulation threshold had been reproducible on multiple determinations before glucagon. In only one of the nine patients was a significant change in stimulation threshold observed after glucagon. In this patient threshold increased by 60 per cent at the 3 minute period but returned to control by 10 minutes.

No significant change in systemic arterial pressure was observed after glucagon. The only side effects noted with glucagon were

pacemakers by determining the drug's effect on the rate of this pacemaker. Seven patients had complete heart block, four with QRS complexes of normal duration. Two patients had nodal pacemakers with apparently normal A-V conduction. One of these latter patients had a digitalis induced nodal tachycardia whereas the other had persistent sinoatrial asystole but could be paced from the atrium up to a rate of 140 per minute with no evidence of impaired A-V conduction. In patients with intracardiac pacemakers the spontaneous rate was determined during cessation of pacing and only those patients who could tolerate this without developing symptoms were selected for study.

The effect of glucagon on threshold for stimulation was determined in nine patients with temporary transvenous pacemakers. A Cordis Synchrocor II which permits stepwise changes in current flow of 0.1 ma was used as the external power source. The minimal milliamperage necessary for stimulation was determined on several occasions and thereafter was maintained at the lowest setting which permitted constant pacing; pacing rate ranged from 70 to 80 beats per minute. After glucagon administration the minimal milliamperage necessary for stimulation was again determined at each of the periods designated below. The stimulation threshold was determined from the settings on the power supply and therefore was not necessarily that delivered to the endocardium.

Six patients were receiving a digitalis glycoside, but in only one was this substantiated as being a causative or contributing factor to the arrhythmia. No patient had suffered a myocardial infarction within the preceding six weeks and with the exception of the patient with nodal tachycardia, the existing cardiac rhythm had been stable for at least seven days preceding the study.

Indirect or direct brachial arterial pressure and standard Lead II of the electrocardiogram (ECG) were recorded in all patients. Furthermore, in two patients with first degree heart block, atrial, ventricular and His bundle potentials were recorded with intracardiac electrodes utilizing the technique described by Damato and associates.¹⁸

In all patients an infusion of 5 per cent glucose in water was begun and, after control measurements were obtained, 5 mg of glucagon dissolved in normal saline was given intravenously over 30 seconds. Measurements of blood pressure, 30 second recordings of the standard ECG and, when appropriate, stimulation threshold were obtained 1, 3, 5, 10, 15 and 30 minutes after completion of the injection. In the patients with first degree heart block, brief recordings at a paper speed of 100 mm per second were also obtained at these time periods.

Results

The clinical data for each individual are given in Table I.

The individual results of the effect of glucagon on A-V conduction are presented in Table II. No clinically significant change in ventricular rate occurred in patients with atrial fibrillation following glucagon injection. One of these patients (E.T.) required propranolol (80 mg per day) as well as digoxin to control his ventricular response before glucagon. In the four patients with first degree heart block the P-R interval increased by only 10 msec in one, was unchanged in another and decreased by a maximum of 15 msec in the remaining two. In the latter two patients recordings from intracardiac electrodes revealed that the decrease in P-R interval which was maximum at the 1 minute period and thereafter returned toward control resulted from a decrease in the P-His bundle interval with an unchanged H-Q interval. In none of the patients with second degree block was there a significant change in conduction following glucagon administration. Although not included in Table II, glucagon did not restore A-V conduction in any patient with complete heart block.

The effect of glucagon on automaticity is presented in Table III. In three of the four patients with complete heart block and pacemakers above the bifurcation of the bundles no change in the rate of the dominant pacemaker was observed after glucagon. In the remaining patient the rate increased by a maximum of 10 beats per minute at the 1 minute period and thereafter returned toward control values. Glucagon did not alter the rate of the dominant

Table III Effect of glucagon on automaticity

Patient	Ventricular rate (beats/min)						
	Control	Minutes after injection					
		1	3	5	10	15	30
First block normal QRS							
M.R.	44	—	44	46	44	44	—
R.Vc	45	48	45	45	45	42	43
R.C.	60	60	66	64	60	60	—
M.G.	59	56	60	54	54	56	57
Wide QRS							
E.R.	37	37	37	37	37	37	35
G.T.	35	38	38	38	35	34	34
M.O.	72	72	72	72	72	72	—
Nodal tachycardia							
C.F.	136	136	136	136	142	140	136
Sinus arrest nodal pacemaker							
V.S.	44	44	44	48	48	50	50

Table IV Effect of glucagon on stimulation threshold

Patient	Control (ma)	Minutes after injection					
		1 (ma)	3 (ma)	5 (ma)	10 (ma)	15 (ma)	30 (ma)
A.C.	1.3	1.3	2.1	1.9	1.3	1.3	1.3
W.E.	0.8	0.8	0.8	0.8	0.8	0.8	0.8
E.C.	1.0	1.2	1.0	1.2	1.3	1.1	1.1
V.S.	10.0	10.5	10.5	10.0	10.0	10.0	10.1
M.G.	8.0	8.0	8.0	7.0	7.0	8.0	8.0
R.C.	0.8	0.8	0.8	0.8	0.8	0.8	0.8
E.R.	0.9	0.8	0.9	0.9	1.0	1.0	1.0
R.V.	2.3	2.4	2.4	2.4	2.3	2.2	2.3
M.O.	0.8	0.8	0.8	0.9	0.8	0.8	—

In a single study in man glucagon was reported to decrease first-degree heart block and to restore sinus rhythm in patients with complete heart block or supraventricular tachycardia.¹⁹ However these patients had cardiogenic shock or acute left ventricular failure at the time of the study and the authors attributed the electrophysiologic improvement to the positive inotropic effects of the hormone.

The lack of effect of glucagon on nodal and ventricular pacemakers in man also is

in contrast to its effect on nodal^{11,18} and ventricular automaticity^{11,18} in dogs. Enhancement of the latter however has not been a universal observation.¹¹ Others have reported that glucagon at the same dose per unit of body weight produced a greater chronotropic and inotropic effect in dogs than in man²⁰ suggesting that species differences may produce or contribute to these disparate results concerning the drug's electrophysiologic effects.

We are unaware of any report concerning

Table II Effects of glucagon on atrio-ventricular conduction

Patient		Control	Minutes after injection					
			1	3	5	10	15	30
Atrial fibrillation								
V J	Ventricular rate beats per minute	75 80	80	80	76	84	84	76
L H	Ventricular rate beats per minute	70 74	74	70	76	66	66	68
L B	Ventricular rate beats per minute	75 80	80	80	76	84	84	66
L I	Ventricular rate beats per minute	80 84	84	88	84	80	84	86
1 heart block								
M B	Atrial rate	66	76	66	74	74	64	64
	P R interval (m sec)	250	260	260	250	250	250	250
A C	Atrial rate	74	76	74	74	64	64	64
	P R interval (msec)	230	230	230	230	230	230	—
J L	Atrial rate	85	88	94	78	68	80	—
	P R interval (msec)	210	195	210	200	210	210	—
	P H (msec)	165	150	155	155	165	165	—
	H Q	45	45	45	45	45	45	—
C P	Atrial rate	90	93	95	90	90	—	—
	P R interval (msec)	210	195	210	220	220	—	—
	I H	160	145	160	140	140	—	—
	H Q	50	50	50	50	50	—	—
2 heart block								
W L	Atrial rate	68	78	80	78	78	74	67
	Ventricular rate	34	39	40	39	39	37	36
W P	Atrial rate	65	68	71	68	68	64	64
	Ventricular rate	37	36	36	36	36	35	37
E C	Atrial rate	88	100	96	96	94	88	86
	Ventricular rate	44	50	48	48	47	44	43

nausea and vomiting which occurred in two patients

Discussion

With few exceptions glucagon produced no significant change in A V conduction nodal or ventricular automaticity or threshold for stimulation in this study

The lack of effect of glucagon on A V conduction in these patients is in contrast to that observed in animals where glucagon enhanced conduction or restored 1:1 conduction in animals in which 2:1 block had been produced. In this latter study it was observed that glucagon decreased the P H bundle interval without affecting the H Q

interval. In two patients in the present study in whom His bundle electrograms were obtained the pre-existing block occurred proximal to the His bundle deflection. In both glucagon shortened the P H interval without affecting the H Q interval. The maximum shortening however was only 15 msec and was brief in duration.

Whitsitt and Lucchesia¹⁴ also reported that glucagon reversed the depression of A V conduction produced by propranolol in dogs. In our study no increase in ventricular rate was observed after glucagon in the one patient with atrial fibrillation receiving propranolol in addition to digoxin to control his ventricular rate.

- receptor blockade with propranolol *Circ. Res.* 29: 89 1968.
6. Parmley W W, Chick G and Sonnenblick E H Cardiovascular effects of glucagon in man *N Engl J Med* 279 12 1968
7. Klein S W, Morch J E and Mahon W A Cardiovascular effects of glucagon in man *Can. Med. Assoc. J* 98 1161 1968
8. Liebart, J W, Barold S S, Cohen L S, Hildner E J and Samet, P Cardiovascular effect of glucagon in man *Am J Cardiol* 22 66 1968
9. Williams J F Jr, Childres R H, Chip J V and Border J F Hemodynamic effect of glucagon in patients with heart disease *Circulation* 39:38 1969
10. Nord H J, Fontane, A L and Williams J F Jr Treatment of congestive heart failure with glucagon *Ann. Intern. Med* 72 649 1970
11. Wilken, D E L and Loeff R. Glucagon in resistant heart failure and cardiogenic shock. *Lancet* 1 1315 1970
12. Vandermark C R and Reynolds E W Clinical evaluation of glucagon by continuous infusion in the treatment of low cardiac output states *Am. HEART J* 9 481 1970
13. Seiner C, Wit A L and Damato A N Effects of glucagon on atrioventricular conduction and ventricular automaticity in dogs *Circ. Res.* 41 167 1969
14. Whitsett L S and Lucches B III Effects of beta receptor blockade and glucagon on the atrioventricular transmission system in the dog. *Circ. Res.* 23 585 1968
15. Lucches B R, Stutz D R and Winfield R A. Glucagon: Its enhancement of atrio-ventricular nodal pacemaker activity and failure to increase ventricular automaticity in dogs *Circ Res* 23:183 1969
16. Hurwitz R A. Effect of glucagon on dogs with acute and chronic heart block. *Am. HEART J* 81 644 1971
17. Wilkerson R D, Pruett J K and Woods E F. Glucagon-enhanced ventricular automaticity in dogs. Its concealment by positive chronotropism *Circ Res* 29 616 1971
18. Damato A N, Lau S H and Heilant R W. Study of atrioventricular conduction in man using electrode catheter recording of His bundle activity. *Circulation* 39 787 1969
19. Robert W and Humair L. The cardiotonic effect of glucagon. Clinical study and therapeutic indications. *Schweiz. Med. Wochr* 100 1345 1970
20. Manchester J H, Parmley W W, Matloff J M, Leidlke A J, LaRosa P J, Hermann M V, Sonnenblick E H and Gorlin R. Effects of glucagon on myocardial oxygen consumption and coronary blood flow in man and in dog. *Circulation* 41 579 1970
21. Gold H K, Prindle K H, Levey G S and Epstein S E. Effects of experimental heart failure on the capacity of glucagon to augment myocardial contractility and activate adenylyl cyclase. *J Clin Invest.* 49 999 1970

the effect of glucagon on the threshold for ventricular stimulation. In eight of the nine patients of this study no change in threshold was observed after glucagon. Thus the administration of glucagon to patients requiring ventricular pacemakers is unlikely to cause pacing failure. However, since a 60 per cent increase in stimulation did occur in one patient, careful observation should be given if glucagon is employed under these conditions.

It has been observed that the positive inotropic effect of glucagon is reduced or absent in the presence of chronic congestive heart failure.^{10, 11} Although hospitalization was precipitated by the development of heart failure in several of our patients, all were clinically well compensated at the time of the study. Furthermore, the majority of patients had not developed this complication. Thus the failure to observe significant electrophysiologic changes after glucagon cannot be attributed to the presence of chronic congestive failure.

To avoid the depressant action of phenol which was contained in the commercially available diluent, glucagon was dissolved in normal saline immediately before administration to each patient. The increase in sinus rate which occurred in most patients with sinus rhythm indicates that the glucagon administered was pharmacologically active. Furthermore, glucagon from the same lot was dissolved in saline and added to the bath of isometrically contracting cat papillary muscles (final concentrations 20 μ g per milliliter), a near doubling of the force of contraction was observed.

The dose of glucagon selected for this study is similar to that employed in previous studies of the cardiovascular effects of glucagon in man and approaches the maximal amount that can be given by rapid injection without an inordinate degree of nausea or vomiting. Whether different results would be obtained with larger amounts or continuous infusions of this agent is unclear. Similarly, patients with disorders of impulse formation or conduction caused by conditions other than those afflicting our patients may respond in a different manner. It must also be appreciated that glucagon can lower serum potassium concentrations,^{6, 9} an undesirable occurrence in patients receiving digitalis glycosides.

Nevertheless, the present results, combined with the lack of significant arrhythmias observed in any of the previous studies of glucagon in man, indicate that the direct electrophysiologic effects of this hormone are unlikely to be clinically important.

Summary

Glucagon (5 mg) was injected intravenously into patients with stable disorders of impulse formation or conduction during electrocardiographic monitoring. The ventricular rate did not change significantly in any of the four patients with atrial fibrillation nor did glucagon alter A-V conduction in any of the three patients with second degree heart block. In two patients with first degree heart block the P-R interval shortened briefly by a maximum of 15 msec, the shortening due entirely to a decrease in the P-His bundle interval with no change in the H-Q interval. In two additional patients with first degree block the P-R interval remained essentially unchanged. In seven patients with complete heart block, four with QRS complexes of normal duration, glucagon did not affect the rate of the spontaneous pacemaker. Similarly in two patients with nodal pacemakers and normal A-V conduction, glucagon was without significant effect. In only one of nine patients with a functioning temporary transvenous pacemaker was a significant change in the threshold for stimulation observed.

These results indicate that glucagon is unlikely to produce electrophysiologic effects of clinical importance in patients with impaired impulse formation or conduction.

REFERENCES

- 1 Farah A and Tuttle R. Studies on the pharmacology of glucagon. *J Pharmacol Exp Ther* 129:49 1960.
- 2 Regan T J, Lehan P H, Hennen D H, Behar A and Hellem H K. Myocardial metabolic and contractile response to glucagon and epinephrine. *J Lab Clin Med* 63:638 1964.
- 3 Whitehouse F W and James T N. Chronotropic action of glucagon on the sinus node. *Proc Soc Exp Biol Med* 122:823 1966.
- 4 Lucchesia H R. Cardiac actions of glucagon. *Circ Res* 22:777 1968.
- 5 Glick G, Parmley W W, Wechsler A S and Sonnenblick L H. Glucagon: Its enhancement of cardiac performance in the cat and dog and persistence of its inotropic actions despite beta

Vol. 24
No. 3

leads during the control period and at the end of each 30 minute interval simultaneous with the above blood samples. Time marks were also recorded (10 and 100 msec) using a model 184 Tektronix time mark generator. These records were analyzed for changes in duration and/or configuration of P R QRS QT ST segment and T wave.

Results

There was a relatively wide range in blood levels of lidocaine (Fig. 1) at any given infusion concentration despite identical infusion techniques in all patients. Although no patient was known to have intrinsic liver disease several of the patients were in a state of minimal congestive heart failure. Nevertheless the highest levels were obtained in the patient without any evidence of cardiac or hepatic decompensation (8.2 mg per liter Patient S B see Fig. 2). There was however a relatively linear relationship between the infusion concentration and mean serum lidocaine level (Fig. 1). Two patients showed clinical signs of toxicity manifest as lethargy but did not demonstrate a decrease in arterial blood pressure even at toxic blood levels. Despite the variation in heart rate for any individual over the 2½ hour study period no definite trend emerged with relation to serum lidocaine levels (Table I).

Similarly the I R interval QRS duration and Q T interval showed no consistent change which would correlate with the patients determined serum lidocaine level (Table I).

Even in those patients subsequently found to have serum lidocaine levels generally accepted to be in the toxic range no change was found in any of the above parameters. In addition the QRS and T vectors also showed no change in correlation with the serum lidocaine level. Fig. 2 shows an example in one of our patients of the series of orthogonal lead recordings made during one of experimental infusion studies.

Discussion

Clinical properties. Lidocaine, a local anesthetic has been found to possess significant antiarrhythmic effects. It was ini-

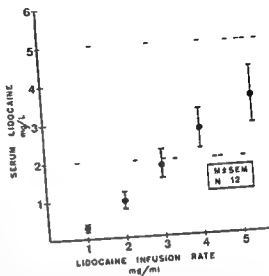


Fig. 1 Serial measurements of serum lidocaine levels. The lidocaine infusion rates are plotted on the horizontal axis and the corresponding serum lidocaine levels at the end of a ½ hour infusion period are plotted on the vertical axis.

tially anticipated that these properties would be similar if not identical with procaine amide which is another local anesthetic of very similar structure. However early clinical investigation showed considerable deviations in these two agents antiarrhythmic spectrum. Procaine amide was found to be effective against premature atrial junctional and ventricular beats as well as various supraventricular arrhythmias.¹⁶ Lidocaine in contrast was found to be ineffective against atrial arrhythmias.^{17,18} Furthermore procaine amide in both therapeutic and toxic levels was shown to prolong A V conduction intraventricular conduction and ventricular repolarization.^{19,20} However a recent clinical study by Rosen and associates¹⁴ showed lidocaine to have minimal if any change in A V or ventricular conduction when a single or repeat bolus of lidocaine in generally accepted therapeutic doses (1 to 2 mg per kilogram) was given intravenously.¹⁴ This dosage regimen may be expected to produce blood levels of 1 to 10 mg per liter for at least 30 minutes in the absence of significant congestive heart failure or liver disease.²¹

Electrophysiologic properties. Lidocaine and procaine amide have likewise been contrasted in their effects on action potential

Effect of lidocaine on the scalar orthogonal electrocardiogram

Alan I Kermater, MD
H Hayakawa, MD
William J Mandel, MD
Los Angeles, Calif

Lidocaine was first used for the treatment of cardiac arrhythmias in 1959.¹ Since that time it has been used increasingly for the treatment of ventricular ectopic beats associated with acute myocardial infarction and arrhythmias secondary to digitalis toxicity.²⁻⁴ The drug's relatively minor negative inotropic effect when compared to procaine amide or quinidine makes it particularly desirable as an antiarrhythmic agent in acute myocardial infarction.⁵⁻⁷

Extensive electrophysiologic studies are available on the effects of lidocaine and the relationship to its clinical antiarrhythmic properties.⁸⁻¹⁴ Characteristic findings noted in concentrations considered therapeutic have been shortening of action potential duration and effective refractory period as well as a possible increase in intraventricular conduction velocity. It has therefore been suggested that in the clinical setting lidocaine may shorten both intraventricular conduction and the Q-T interval of the standard electrocardiogram (ECG). Based on such experimental data it was elected to study the clinical effects of graded doses of

intravenous lidocaine on the body surface ECG.

Methods

Twelve patients (five female, seven male, age range 44 to 75) were selected for study on the basis of the following criteria: sinus rhythm, normal A-V and intraventricular conduction and refraining from drugs with known effects on the ECG for at least 72 hours prior to study. All patients had a history of recurrent ventricular premature beats.

After obtaining informed consent lidocaine HCl was infused at a constant rate by Harvard infusion pump at successive rates of 1, 2, 3, 4, and 5 mg per minute for half hour intervals respectively. Serum lidocaine levels^{15,16} were determined at each half hour interval just prior to increasing the infusion rate. Body surface ECG's were obtained at a 200 mm paper speed (Hewlett Packard No 1505 A three-channel ECC amplifier; Honeywell No 1508 oscillograph) by use of a simultaneous display of the scalar X, Y, and Z Frank orthogonal

From the Department of Cardiology, Cedars-Sinai Medical Center and the Department of Medicine, University of California, Los Angeles, Calif.
Supported in part by National Institutes of Health Grant HL 05048 in Medical Cardiology and United States Public Health Service Grant 5 S01 RR 05468.
Received for publication on Nov. 22, 1971.
Reprint requests to William J. Mandel, MD, Department of Cardiology, Cedars of Lebanon Hospital, 4833 Forest Avenue, Los Angeles, Calif 90029.
*Performed by L. A. Boyce, PhD, Astra Pharmaceutical Co., Worcester, Mass.

leads during the control period and at the end of each 30 minute interval simultaneous with the above blood samples. Time marks were also recorded (10 and 100 msec) using a model 184 Tektronix time mark generator. These records were analyzed for changes in duration and/or configuration of I P R QRS Q T ST segment and T wave.

Results

There was a relatively wide range in blood levels of lidocaine (Fig 1) at any given infusion concentration despite identical infusion techniques in all patients. Although no patient was known to have intrinsic liver disease several of the patients were in a state of minimal congestive heart failure. Nevertheless the highest levels were obtained in the patient without any evidence of cardiac or hepatic decompensation (8.2 mg per liter Patient S B see Fig 2). There was however a relatively linear relationship between the infusion concentration and mean serum lidocaine levels (Fig 1). Two patients showed clinical signs of toxicity manifest as lethargy but did not demonstrate a decrease in arterial blood pressure even at toxic blood levels. Despite the variation in heart rate for any individual over the 2½ hour study period no definite trend emerged with relation to serum lidocaine levels (Table I).

Similarly the P R interval QRS duration and Q T interval showed no consistent change which would correlate with the patients determined serum lidocaine level (Table I).

Even in those patients subsequently found to have serum lidocaine levels generally accepted to be in the toxic range no change was found in any of the above parameters. In addition the QRS and T vectors also showed no change in correlation with the serum lidocaine level. Fig 2 shows an example in one of our patients of the series of orthogonal lead recordings made during one of experimental infusion studies.

Discussion

Clinical properties. Lidocaine a local anesthetic has been found to possess significant antiarrhythmic effects. It was in-

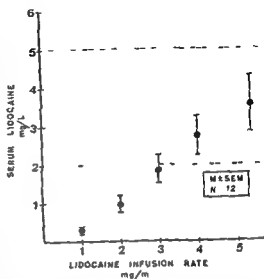


Fig 1 Serial measurements of serum lidocaine level. The lidocaine infusion rates are plotted on the horizontal axis and the corresponding serum lidocaine levels at the end of a ½ hour infusion period are plotted on the vertical axis.

tially anticipated that these properties would be similar if not identical with procaine amide which is another local anesthetic of very similar structure. However early clinical investigation showed considerable deviations in these two agents antiarrhythmic spectrum. Procaine amide was found to be effective against premature atrial junctional and ventricular beats as well as various supraventricular arrhythmias.¹⁶ Lidocaine in contrast was found to be ineffective against atrial arrhythmias.^{17,18} Furthermore procaine amide in both therapeutic and toxic levels was shown to prolong A V conduction intraventricular conduction and ventricular repolarization.^{16,19,20} However a recent clinical study by Rosen and associates²¹ showed lidocaine to have minimal if any change in A V or ventricular conduction when a single or repeat bolus of lidocaine in generally accepted therapeutic doses (1 to 2 mg per kilogram) was given intravenously.²¹ This dosage regimen may be expected to produce blood levels of 1 to 10 mg per liter for at least 30 minutes in the absence of significant congestive heart failure or liver disease.²¹

Electrophysiologic properties. Lidocaine and procaine amide have likewise been contrasted in their effects on action potential

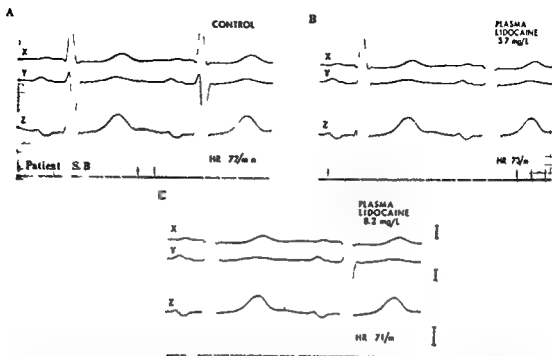


Fig. 2 The effect of lidocaine on the ECG. Scalar Frank orthogonal leads (X, Y, and Z) are displayed in each panel. Time lines are recorded at the bottom of each panel and recur every 10 m sec and 100 m sec. Voltage (0.5 mv) calibrations for each lead are shown to the right of panel C. Note the slight decrease in sinus rate without significant change in any other variable.

characteristics of isolated Purkinje fiber-ventricular muscle preparations.^{8,11,12} Procaine amide has been shown to increase slightly the action potential duration (APD) of both Purkinje and ventricular muscle fibers and increase the effective refractory period (ERP) of these tissues.² Lidocaine, in contrast (in concentrations thought to represent therapeutic blood levels), has been shown to decrease the APD as well as ERP of both Purkinje and ventricular muscle fibers.^{8,11,12} Both these drugs however have been shown to have a $\Delta\text{APD}/\Delta\text{ERP}$ of <1 .^{8,11,12} Nevertheless previous studies^{8,9} refer to lidocaine as shortening of the APD as a possible important mechanism in this drug's antiarrhythmic action. Since decremental conduction has been suggested to be an important factor in reentry mechanism lidocaine's effect on the APD would, in part, serve to abolish arrhythmias sustained by reentry.³ The decrease in the APD previously described consists of a shortened phase 2 with an increased slope of phase 2 and phase 3 of the Purkinje fiber and ventricular muscle action potential.^{8,11} It is generally accepted that the ST segment of the ECG in the

intact heart corresponds to phase 2 of the action potential.⁴ If APD did, in fact, shorten with therapeutic levels of lidocaine, then in our study the ST segment should have shortened, at least at our highest lidocaine blood levels. The present results suggest that this effect may not be a significant mechanism of lidocaine's antiarrhythmic action in man when given in therapeutic doses. It is however possible that the more pronounced effects seen *in vitro* in Purkinje fibers compared to ventricular muscle may, in fact, be responsible for the lack of significant repolarization changes following lidocaine.

In our study with the Frank scalar orthogonal display we used the longest measurement from these leads to preclude any change in vector from affecting the measurement. It therefore appears from our data that the therapeutic dose range in man may more closely approximate a lower lidocaine level than that assumed by the previous *in vitro* studies.^{8,11} Lidocaine at between 5×10^{-6} and 1×10^{-7} M per liter, described by these investigators, produced no change in the APD or membrane responsiveness. An increase in membrane

Table I Lidocaine infusion rate (mg/min)

Parameter	Control	1 mg/min	2 mg/min	3 mg/min	4 mg/min	5 mg/min
PP (msec)	194 ± 77	835 ± 107	815 ± 73	804 ± 67	806 ± 110	196 ± 132
PR (msec)	174 ± 15	172 ± 21	171 ± 18	171 ± 17	172 ± 22	170 ± 19
QRS (msec)	97 ± 9	101 ± 10	100 ± 10	101 ± 9	99 ± 12	97 ± 10
Q-T (msec)	442 ± 58	433 ± 49	436 ± 67	473 ± 59	427 ± 55	410 ± 60
BP (mm Hg)						
Systolic	133 ± 9	134 ± 8	136 ± 11	140 ± 10	139 ± 10	138 ± 12
Diastolic	88 ± 3	88 ± 3	93 ± 3	92 ± 3	97 ± 4	90 ± 3

M ± SEM N = 12

Values are means ± SEM of 12 patients in each group. The values are compared with the control values (t test for paired samples).

responsiveness at 1×10^{-5} would increase conduction and thus prevent decremental conduction and the resultant reentry. If our proposed therapeutic in vivo concentrations are used this effect on membrane responsiveness would therefore not be present. However the shortening effect of lidocaine on refractoriness especially the relative refractory period was present in vitro even at the lower concentrations. This effect would possibly serve to decrease the chance for local decremental conduction and therefore diminish the incidence of ectopic beats. Finally our proposed therapeutic in vitro concentration would still decrease the automaticity of phase 4 depolarization in Purkinje fibers according to previous data.⁸

Blood levels. Since lidocaine has no deleterious effect on the ECG and only slight negative inotropic effects in the low toxic range,¹ the chief clinical guide to toxic blood levels has been the central nervous system effects including drowsiness incoordination, jitteriness and frank convulsions. Hepatic metabolism is the major pathway for removal of the drug and Thompson and co-workers¹ have recently emphasized the danger of encountering toxic levels in patients in congestive heart failure with hepatic engorgement. The experience in our patients (Fig. 1) demonstrates the wide range of serum levels after constant infusion of this drug in patients without clinical hepatic disease or congestive heart failure. Stable serum levels even with constant infusion techniques would not be expected however for 8 to 12 hours.²² It would be anticipated that the standard gravity drip used in most cardiac care units to infuse

lidocaine would further tend to increase the variability in blood levels actually achieved in patients. If control of arrhythmias in a given patient requires levels just under those producing central nervous system symptoms it would seem imperative that a more accurately controlled method of infusion be used.

Summary

In summary our data indicate that therapeutic serum levels of lidocaine demonstrate no electrocardiographic change and especially no shortening of the Q-T interval. This suggests that the therapeutic in vitro lidocaine level may be less than previously assumed.

REFERENCES

1. Hitchcock P and Keown K. K. The management of cardiac arrhythmias during cardiac surgery. *South Med J* 52:107 1959
2. Gussell, R. von der Groeben J O Spivack A P and Harrison D C Effect of lidocaine on ventricular arrhythmias in patients with coronary heart disease. *Br J Med* 2:7 1215 1967
3. Jewitt D E Hishon Y and Thomas M. Lidocaine in the management of arrhythmias after acute myocardial infarction. *Lancet* 1 266 1968
4. Hilm K J and Peran T J. Relative effectiveness of antiarrhythmic drugs in treatment of digitalis-induced ventricular tachycardia. *Am J Cardiol* 76:363 1968
5. Lieberman N A Harris R S Katz R I Lipschutz H M Dolgin M and Fisher V J. The effects of lidocaine on the electrical and mechanical activity of the heart. *Am J Cardiol* 22:375 1968
6. Austen W G and Moran J M. Cardiac and peripheral vascular effects of lidocaine and procainamide. *Am J Cardiol* 16:101 1965
7. Harrison D G. Scoville J H and Morrow

- A G The arrhythmic properties of lidocaine and procaine amide *Circulation* 28:486 1963
- 8 Bigger J T Jr and Mandel W J Effect of lidocaine on the electrophysiological properties of ventricular muscle and Purkinje fibers *J Clin Invest* 49:63 1970
- 9 Bigger J T Jr and Mandel W J Effect of lidocaine on conduction in canine Purkinje fibers and at the ventricular muscle-Purkinje fiber junction *J Pharmacol Exp Ther* 172:239 1970
- 10 Mandel W J and Bigger J T Jr Electrophysiologic effects of lidocaine on isolated canine and rabbit atrial tissue *J Pharmacol Exp Ther* 178:81 1971
- 11 Davis L D and Temte J V Electrophysiological actions of lidocaine on canine ventricular muscle and Purkinje fibers *Circ Res* 24:639 1969
- 12 Sugimoto T, Schaal S F, Dunn N V, and Wallace A G Electrophysiologic effects of lidocaine in awake dogs *J Pharmacol Exp Ther* 166:146 1969
- 13 Singh B N and Vaughn Williams E M Effect of altering potassium concentration on the action of lidocaine and diphenylhydantoin on rabbit atrial and ventricular muscle *Circ Res* 29:286 1971
- 14 Rosen K M, Liu S H, Weiss M B, and Damato A N The effect of lidocaine on atrioventricular and intraventricular conduction in man *Am J Cardiol* 25:1 1970
- 15 Keenaghan J B The determination of lidocaine and procaine in whole blood by gas chromatography *Anesthesiology* 29:110 1968
- 16 Bigger J T Jr and Heissenbittel K H The use of procaine amide and lidocaine in the treatment of cardiac arrhythmias *Prog Cardiovasc Dis* 11:515 1969
- 17 Flenskjeld Jensen E and Sindpe E Lidocaine as an antiarrhythmic agent *Acta Med Scand* 185:297 1969
- 18 Grossman J I, Lubow L A, Frieden J, and Rubin I L Lidocaine in cardiac arrhythmias *Arch Intern Med* 121:396 1968
- 19 Woshe H, Belford J, Fastier F A, and Brooks C McC Effect of procaine amide on excitability, refractoriness and conduction in the mammalian heart *J Pharmacol Exp Ther* 107:135 1953
- 20 Brooks C McC, Hoffman B F, Suckling E C, and Orin O Excitability of the heart *New York* 1955 Grune & Stratton Inc
- 21 Thompson P D, Rowland M, and Melmon K L The influence of heart failure, liver disease and renal failure on the disposition of lidocaine in man *Am Heart J* 82:417 1971
- 22 Hoffman B F The action of quinidine and procaine amide on single fibers of dog ventricle and specialized conducting system *Am Acad Bras Cienc* 29:365 1968
- 23 Singer D H, Lazzari R, and Hoffman B F Interrelationships between automaticity and conduction in Purkinje fibers *Circ Res* 21:537 1967
- 24 Hecht H H Some observations and theories concerning electrical behavior of heart muscle *Am J Med* 30:720 1961
- 25 Hoffman B F and Cranefield P F *Electrophysiology of the heart* New York 1960 McGraw Hill Book Co Inc
- 26 Fittle T and Hayes A Kinetics of lidocaine in blood *Clin Res* 10:334 1970

Effects of ouabain on cardiac output and pulmonary blood flow in dogs

Elmer Treat, MD

Harvey Ulano PhD

Marc Pfeffer BA

Walter Massion MD

Linda L. Shanbour PhD

Eugene D. Jacobson MD

Oklahoma City Okla and Houston Tex

In 1926 Harrison and Leonard¹ reported that digitalis caused a paradoxical decrease in the cardiac output of dogs with nonfailing hearts despite increased efficiency of systolic contraction. More recently several reports²⁻⁴ have confirmed these findings in normal human subjects. In other canine studies Dock and Tainter⁵ noted that digitalis caused decreased central venous pressure, increased systemic arterial and portal venous pressures, and an increased hepatosplenic volume. They postulated that hepatic vein constriction trapped blood in the abdominal viscera accounting for a decreased venous return. Others^{6,7} subsequently confirmed these findings. Cotten and Stopp⁸ using a canula, rotameter in the aortic arch of dogs with nonfailing hearts reported that ouabain increased contractility, peripheral resistance and blood pressure but that it decreased left ventricular output, heart rate and arterial pressure. When left atrial pressure was maintained by infusion of

blood, ventricular output and stroke work increased. Ross and associates⁹ observed similar responses in dogs on cardiopulmonary bypass who were given acetylcholine.

Recently Harrison and co-workers¹⁰ have studied the effects of ouabain on the splanchnic circulation of dogs; they have noted a significant precapillary constriction but no significant changes in splenic and gut weight or liver blood volume. Moreover, some recent data on normal human subjects^{11,12} have failed to substantiate earlier reports of a decreased cardiac output after digitalization. In light of these reports we undertook the present study to quantify cardiocirculatory responses to ouabain in dogs with nonfailing hearts by means of direct flowmetry on the aortic arch and pulmonary artery. To further evaluate the possibility that ouabain evokes pulmonary pooling of blood we also studied a constantly perfused isolated lung lobe preparation.¹³

From the Departments of Surgery, Physiology and Biophysics, University of Oklahoma Medical Center, Oklahoma City, Okla., and the Department of Physiology, University of Texas Medical School at Houston, Houston, Texas. Supported by Department of Defense Grant 555 and United States Army Grant DADA 17-69 C 9025.

Received for publication March 3, 1973.

Reprint requests to Eugene D. Jacobson, MD, Program in Physiology, University of Texas Medical School, Houston, Texas 77030.

Methods

Eighteen mongrel dogs weighing 16 to 24 kilograms were divided into three equal groups for study of (a) aortic blood flow, (b) pulmonary artery blood flow, and (c) volume changes and pressure in the isolated lung lobe. All dogs were anesthetized with intravenously injected sodium pentobarbital (30 mg per kilogram). After endotracheal intubation each animal was placed on a respirator (Harvard Apparatus) with an inspiratory rate set at 14 to 18 cycles per minute and a tidal volume of 250 to 350 ml, depending upon the size of the dog. The right femoral artery was cannulated for measurement of arterial pressure via a strain gauge transducer (Statham). The right femoral vein was cannulated for injection. Lead II of the electrocardiogram was recorded continuously on each dog.

Aortic blood flow group Each of the 6 dogs in this group was subjected to a midline laparotomy and cannulation of the portal vein. Pressure in the portal vein was recorded with a saline manometer. The incision was closed and the animal was then placed in a right lateral decubitus position for a left thoracotomy at the fourth intercostal space. The pericardium was incised and the proximal aorta was isolated. A 14 or 16 mm (inner diameter) electromagnetic blood flow transducer (Micron) was positioned around the aorta and connected to a flowmeter amplifier (Micron). The left external jugular vein was cannulated with the catheter tip positioned at the level of the right atrium for monitoring central venous pressure (CVP) via a saline manometer. In this series of dogs we recorded aortic blood flow, left ventricular output minus coronary blood flow (AQ), mean systemic arterial blood pressure (SAP), portal venous pressure (PVP), and heart rate (HR) on a polygraph (Sanborn). Total peripheral resistance (TPR) was calculated from (SAP/CVP)/AQ. After a 30 minute period of stabilization, each dog was injected intravenously with 5 ml of the solvent used in the commercial ouabain preparation and was observed for an additional 30 minutes. At the end of this period 5 ml of ouabain (Lilly), 45 μ g per kilogram of body weight was infused for one minute into the right femoral vein. With the end of ouabain

infusion considered as zero time measurements were recorded at 2.5, 5, 7.5, 10, 12.5, 20, and 30 minutes.

Pulmonary artery group Six dogs were subjected to a left thoracotomy in the fourth intercostal space. A catheter was inserted into the right atrium via the jugular vein. The pulmonary artery was isolated and an electromagnetic flow probe (Micron) of 12 or 14 mm (inner diameter) was positioned around the vessel. Pulmonary artery blood flow (PAQ), SAP, CVP, and HR were recorded. After a period of stabilization, each dog received a 5 ml intravenous injection of ouabain carrier solution and was observed for 30 minutes. Ouabain (45 μ g per kilogram) was then administered intravenously in a 5 ml volume. In both the cardiac output and pulmonary artery groups, blood flow probes were calibrated with canine whole blood.

Isolated lung lobe group Six dogs were subjected to a thoracotomy at the left fifth interspace. The left lower pulmonary artery and vein were isolated and divided. Tygon tubing (1/4 inch inner diameter) was used to cannulate the divided vessels toward the isolated lobe. An arterial reservoir was elevated so that pulmonary artery pressure to the isolated lung lobe was in the range of 10 to 20 mm Hg. After flow was established, the ribs were approximated and the incision was closed by suturing. A chest tube was used with an underwater seal and the animals breathed spontaneously. A peristaltic pump (Sigmamotor) transferred blood from the venous to the arterial reservoir. Mean blood flow was held constant during each experiment. Left lower pulmonary artery and systemic arterial pressures were continuously recorded with pressure transducers (Statham) connected to a 4 channel recorder (Grass). After a period of stabilization 5 ml of ouabain carrier solution was introduced into the arterial reservoir and readings of net volume change across both reservoirs were taken at 2.5, 5, 10, 15, and 20 minutes. After another 10 minutes of stabilization 5 ml of ouabain (50 μ g per kilogram) were introduced into the arterial reservoir and readings were obtained as previously mentioned. Changes in pulmonary artery pressure were directly proportional to changes in pulmonary vascular resistance and a decrease in the level

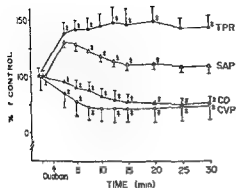


Fig 1 Effects of ouabain on total peripheral resistance (TPR) systemic arterial pressure (SAP) aortic blood flow (CO) and central venous pressure (CVP) over a 30 minute period in 6 dogs. Values are expressed as percentage change (\pm SE) from the values at zero time. Asterisks indicate a significant ($p < 0.05$) difference from zero time values.

of the venous reservoir indicated sequestration of blood in the isolated lung lobe.

The mean values within each group were statistically compared by Duncan's New Multiple Range Test.¹⁴ Differences were considered significant at a probability level of less than 0.05.

Results

Aortic blood flow. Initial control values (including standard error) were SAP 91 ± 3.4 mm Hg, CVP 28 ± 3.4 mm of saline, AQ 1.914 ± 135 ml per minute, TPR 0.047 ± 0.004 mm Hg/ml⁻¹/min⁻¹, PVP 106 ± 8.6 mm of saline, and HR 156 ± 8.0 beats per minute. The administration of ouabain carrier solution elicited no significant changes in any of these measurements. After 30 minutes the following values were recorded: SAP 89 ± 3.3 mm Hg, CVP 27 ± 3.1 mm of saline, AQ 1.595 ± 141 ml per minute, TPR 0.047 ± 0.005 mm Hg/ml⁻¹/min⁻¹, PVP 105 ± 9.1 mm of saline, and HR 159 ± 6.8 beats per minute.

Intravenous injection of ouabain (45 μ g per kilogram) produced significant changes at various times in all parameters during the next 30 minutes (Fig 1). At 2.5 minutes SAP increased 30 per cent to 115 mm Hg ($p < 0.05$). Thereafter SAP gradually declined but was still significantly elevated above control values until 25 minutes after ouabain injection. After the administration of ouabain CVP fell 16

Table 1 Effects of ouabain on portal pressure and heart rate in cardiac output group

Time (min)	Portal venous pressure (mm saline)	Heart rate* (beats/min)
0	105 \pm 9.1	159 \pm 6.8
2.5	107 \pm 9.1	154 \pm 7.7
5.0	110 \pm 9.4†	153 \pm 7.1
7.5	111 \pm 10.0†	146 \pm 7.9†
10.0	112 \pm 9.7†	149 \pm 7.8
12.5	111 \pm 9.3†	149 \pm 8.1
15.0	110 \pm 8.9†	147 \pm 7.9†
20.0	108 \pm 8.8	147 \pm 10.0†
25.0	106 \pm 9.2	149 \pm 10.8
30.0	107 \pm 8.9	149 \pm 9.3

Mean \pm S.E.

† Significantly different from control (time 0).

per cent to 22 mm of saline ($p < 0.05$) and continued to decrease at 12.5 minutes after ouabain injection it was 19 mm of saline ($p < 0.05$). CVP was significantly lower than control values at all times after ouabain was injected. Mean AQ fell 6 per cent at 2.5 minutes to 1.778 ml per minute ($p < 0.05$) and to 1.499 ml per minute (-21 per cent) at 12.5 minutes ($p < 0.05$). At 25 minutes AQ had fallen 25 per cent to 1.426 ml per minute ($p < 0.05$). TPR was significantly elevated at all times after administration of ouabain. It rose rapidly from 0.047 to 0.066 mm Hg/ml⁻¹/min⁻¹ (a 41 per cent increase) at 5 minutes and remained significantly above control values. Mean PVP was 105 mm of saline before ouabain was injected, increasing thereafter (Table 1). PVP was significantly elevated to 110 mm of saline at 5 minutes ($p < 0.05$), it peaked to 112 mm of saline at 10 minutes ($p < 0.05$) and then gradually declined. Mean HR (Table 1) gradually declined after ouabain injection from 159 to 146 beats per minute at 7.5 minutes ($p < 0.05$) after which it began to rise again, reaching 149 beats per minute at 25 minutes.

Pulmonary artery group. Initial control values were SAP 92 ± 6.1 mm Hg, CVP 26 ± 2.6 mm of saline, PAQ 2.423 ± 255 ml per minute, and HR 160 ± 9.3 beats per minute. The administration of ouabain solvent elicited no significant changes in any of the parameters. After 30 minutes of

Table II Comparison of net volume changes across the blood reservoirs in the isolated lower lung lobe after addition of ouabain solvent and ouabain to the arterial reservoir*

Dog No	0	25 min	50 min	100 min	150 min	200 min
<i>Solvent</i>						
1	—	0	+1	+1	+1	+1
2	—	-2	-2	-2	-2	-2
3	—	+2	+4	+3	+2	+1
4	—	0	0	-1	-3	-3
5	—	+6	-3	-2	-1	0
6	—	0	-1	0	0	+1
Mean	—	+1.0	+0.8	+0.3	-0.2	-0.3
SE	—	1.1	1.0	0.8	0.8	0.7
<i>Ouabain</i>						
1	—	+1	+3	+3	+2	-1
2	—	+5	+6	+7	+6	+6
3	—	0	-1	-1	-1	-3
4	—	-1	-2	-4	-3	-4
5	—	+1	-3	0	0	0
6	—	+1	+1	+1	+2	+3
Mean	—	+1.2	+0.7	+1.5	+1.0	+0.2
SE	—	0.8	1.4	1.6	1.3	1.5

*A negative value indicates trapping of blood in the lung lobe; a positive value indicates sequestration in the reservoir.

continuous monitoring, the following values were recorded: SAP 92 ± 5.3 mm Hg, CVP 26 ± 2.8 mm of saline, PAQ $2,455 \pm 259$ ml per minute, and HR 164 ± 8.7 beats per minute. These served as control values.

The administration of ouabain caused significant changes at various times in all parameters during the next 30 minutes (Fig. 2). SAP was increased 29 per cent to 119 mm Hg at 25 minutes after ouabain injection and then gradually fell to 100 mm Hg by 30 minutes. SAP was significantly ($p < 0.05$) elevated above control values at all time periods after drug administration. CVP fell 31 per cent to 18 mm of saline at 25 minutes and continued to decline until 10 minutes when it was 16 mm. Subsequently, it gradually began to return toward the control value. CVP was significantly ($p < 0.05$) decreased at all time periods after ouabain injection. PAQ was significantly ($p < 0.05$) less than control at all time periods. Mean PAQ fell 19 per cent to 1,995 ml per minute at 25 minutes and then gradually returned toward the control value. PAQ was 2,150 ml per minute at 30 minutes (12 per cent

below control). Mean HR decreased after injection of ouabain to 151 beats per minute at 125 minutes ($p < 0.05$) and was still significantly less than control at 30 minutes (148 beats per minute).

Isolated lung lobe group. Addition of ouabain carrier solution to the arterial reservoir in the isolated lung lobe series caused no significant net volume changes, nor did the addition of ouabain (50 μ g per kilogram) to the arterial reservoir (Table II).

However, the ouabain carrier solution decreased pulmonary artery pressure from 194 to 190 mm of saline at 25 minutes. At each subsequent reading up to 20 minutes a significant decrease in pressure was observed (Table III). The addition of ouabain to the arterial reservoir evoked a significant ($p < 0.05$) increase in pulmonary artery pressure at all time periods to 20 minutes (Table III).

Discussion

Rapid digitalization with ouabain decreased aortic blood flow, pulmonary artery blood flow, central venous pressure, and heart rate in anesthetized dogs with non-failing hearts. Ouabain also increased their

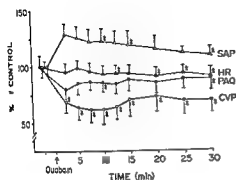


Fig. 3 Effects of ouabain on SAP heart rate (HR) pulmonary artery blood flow (PAQ) and CVP in 6 dogs.

systemic arterial and portal venous pressures and total peripheral and pulmonary vascular resistances. These findings indicate that cardiac glycosides have two major effects on the normal circulation (a) constriction of the precapillary segment and (b) decrease in venous return. However we are unable to identify the locus of sequestered blood.

In other investigations^{5, 17} we have found that ouabain has a direct constrictor effect in the superior mesenteric and carotid arteries of dogs and monkeys. Our results with the isolated lung lobe indicate similar responses in the pulmonary artery. These data coupled with the rise in arterial pressure and total peripheral resistance identify cardiac glycosides as potent arterial vasoconstrictors in most if not all regional circulations of anesthetized animals.

A decrease in venous return with digitalis was reported in the work of Dock and Tainter¹ and was quantified by Cotten and Stopp⁶. Our results utilizing flowmeter transducers to measure the output from left and right ventricles indicate that digitalis decreases these outputs by 10 to 20 per cent within a few minutes. These findings confirm the measurements of Cotten and Stopp⁶ who used a cannulating aortic rotameter. The slopes of decline in the outputs of the left and right heart (Figs 1 and 2) indicate no great discrepancy between flows which might implicate the lung as the site of sequestration; however our measurement of left heart output excluded coronary blood flow which limits our interpretation of these results. We also found that central venous pressure did not

Table III Comparison of mean pulmonary artery pressure changes in the isolated lower lung lobe after addition of carrier solution alone and then ouabain

Time (min)	Pulmonary artery pressure (mm. saline)	
	Solvent alone	Ouabain added†
0	194 ± 13.2	183 ± 14.9
2.5	190 ± 13.5	193 ± 14.3‡
5.0	186 ± 12.8	200 ± 16.6‡
10.0	182 ± 12.6‡	209 ± 18.2‡
15.0	184 ± 14.0‡	208 ± 17.9‡
20.0	184 ± 14.1‡	208 ± 18.2‡

Values presented are the mean ± S.E. for six experiments. † Ouabain was injected 10 min after the start of the experiment. ‡ Data are the mean of six experiments.

increase after injection of the glycoside and that ouabain failed to cause pooling in the isolated lung lobe thereby obviating the likelihood of active trapping of blood in the lung.

Our finding of a small rise in portal pressure with ouabain suggests that the splanchnic region is a possible site of trapped blood; however previous studies from our laboratory indicated no gain in weight of either gut or spleen and no pooling of blood in the liver.¹⁸ The location of the disappearing venous return in the rapidly digitalized dog cannot be identified at present.

Summary

Anesthetized dogs with nonfailing hearts were rapidly digitalized with ouabain. Aortic blood flow, pulmonary blood flow and central venous pressure decreased at approximately equal rates as a function of time. Passive congestion of blood in the lung seems unlikely in view of these findings. In an isolated lower lung lobe ouabain also failed to cause pooling.

Ouabain increased systemic arterial and portal venous pressures and total peripheral resistance as well as increasing pulmonary vascular resistance in the isolated lung lobe. These findings indicate that ouabain is a general precapillary constrictor.

The author wishes to thank Mr Alvin C K Chang and Mrs Paula Downs for technical assistance and Dr Donald Parker for statistical consultation

REFERENCES

- Harrison T R and Leonard B W The effect of digitalis on the cardiac output of dogs and its bearing on the action of the drug in heart disease *J Clin Invest* 31 1926
- Bing R J Marust F M Dammann J F Draper A Heimbecker R Daley R Gerard R and Calazel P Effect of strophanthus on coronary blood flow and cardiac oxygen consumption of normal and failing human hearts *Circulation* 21 513 1950
- Stewart H J and Cohn A E Studies on the effect of the action of digitalis on the output of blood from the heart III *J Clin Invest* 11 917 1932
- Williams M H Zohman L R and Ratner A C Hemodynamic effects of cardiac glycosides on normal human subjects during rest and exercise *J Appl Physiol* 13 417 1958
- Dock W and Truitt M L The circulatory changes after full therapeutic doses of digitalis with a critical discussion of views on cardiac output *J Clin Invest* 8 467 1930
- Katz L N Rodbird S Friend M and Rottersman W The effect of digitalis on the anesthetized dog I Action on the splanchnic bed *J Pharmacol Exp Ther* 62 1 1938
- Nadler J L Berger A R and Ballinger J Action of ouabain on the splanchnic circulation in the dog *J Lab Clin Med* 25:557 1940
- Cotten M DeV and Stopp P E Action of digitalis on the nonfailing dog heart *Am J Physiol* 192 114 1958
- Ross J Braunwald E and Waldhausen J A Studies on digitalis II Extracardiac effects on venous return and on the capacity of the peripheral vascular bed *J Clin Invest* 39 937 1960
- Harrison L A Blaschke J Phillips R S Price W E Cotten M DeV and Jacobson E D Effects of ouabain on the splanchnic circulation *J Pharmacol Exp Ther* 169 371 1969
- Selzer A Hultgren H and Ebner C L Bradley H W and Stone A O Effect of digoxin on the circulation of normal man *Br Heart J* 21 335 1959
- Dresdale D T Luceoglu Y Z Nichten R J Schultz M and Langer M Effects of inosin on cardiovascular hemodynamics Acute digitalizing dose in subjects with normal hearts and with heart disease without failure *Am J Cardiol* 18 88 1959
- Kux M and Masson W H Effects of E coli organisms on hemodynamics of the dog lung *Ann Surg* 173 116 1971
- Steel R G D and Torrie J H Principles and procedures of statistics New York 1960 McGraw Hill Book Co Inc
- Treat E Ulano H B and Jacobson E D Effects of intra arterial ouabain on mesenteric and carotid hemodynamics *J Pharmacol Exp Ther* 179 144 1971
- Ulano H B Treat E Chang A C K Jacobson E D Splanchnic circulatory responses to ouabain in shock *Surgery* 70 618 1971
- Shanbour L L Jacobson E D Brobmann G F and Hinshaw L B Effects of ouabain on splanchnic hemodynamics in the rhesus monkey *Am Heart J* 71 511 1971

Ventricular responses to hypoxemia following chemoreceptor denervation and adrenalectomy

Robert A Achter MD
S Evans Downing MD
New Haven Conn

There is abundant evidence to support the view that preservation of ventricular function during acute systemic hypoxia is in part attributable to a concomitant elevation in the level of adrenergic stimulation.¹⁻⁴ The system or systems responsible for transduction of these responses has not been fully established. Principal consideration has focused on three major areas: the peripheral chemoreceptors, the central nervous system, and release of catecholamines from the adrenal medulla.

It has been suggested that the carotid chemoreceptors are a major sensory system which when stimulated by reduced oxygen tension will signal a reflex increase of sympathetic outflow to the heart.⁴ However subsequent studies have failed to support this conclusion.⁵⁻⁸ Evidence that the carotid chemoreceptors are relatively more important for respiratory regulation and that aortic arch chemoreceptors have a more profound effect on the circulation¹⁰ suggests that the latter may elicit a qualitatively different pattern of autonomic (efferent) discharge. This idea is consistent with the findings of Stern and Rapoport⁹ who showed that chemical stimulation of

aortic arch chemoreceptor tissue with nicotine bitartrate leads to a reflex increase of myocardial contractility and that this response is reduced or abolished by sectioning the afferent fibers by vagotomy.

In view of the above findings this study was undertaken in an effort to determine if hypoxic stimulation of the aortic chemoreceptors could be shown to contribute to a reflex increase of adrenergic stimulation of the heart during systemic hypoxemia. A preliminary report on these findings has appeared.¹¹

Methods

Adult mongrel cats weighing 2.7 to 3.8 kilograms were anesthetized with intra-peritoneal pentobarbital 30 mg per kilogram of body weight. A tracheostomy was performed and the cervical vagi were loosely looped. In animals subjected to adrenalectomy a midline laparotomy was then performed and the right adrenal gland was removed. The left adrenal gland was dissected from the surrounding connective tissue and a loose ligature snare was placed around its afferent and efferent vessels. The free end of the ligature snare was

From the Department of Pediatrics and Physiology, Yale University School of Medicine, New Haven, Conn.
This work was supported in part by United States Public Health Service Research Grants HE-08659, HE-10949 and by Research Career Development Grant A-04548 (Dr. Downing) from the National Heart Institute.

Received for publication Dec. 2, 1971.

Reprint requests to S. Evans Downing, MD, Assistant Professor of Pathology, Department of Pathology, Yale University School of Medicine, 330 Cedar Street, New Haven, Conn. 06510.

The author wishes to thank Mr Alvin C K Chung and Mrs Paula Downs for technical assistance and Dr Donald Parker for statistical consultation.

REFERENCES

- Harrison T R and Leonard B W The effect of digitalis on the cardiac output of dogs and its bearing on the action of the drug in heart disease *J Clin Invest* 31:1926
- Bing R J Marust F M Dammann J F Draper A Hemmbecker R Daley R Gerard R and Calazel P Effect of strophanthus on coronary blood flow and cardiac oxygen consumption of normal and failing human hearts *Circulation* 24:513 1950
- Stewart H J and Cohn A E Studies on the effect of the action of digitalis on the output of blood from the heart III *J Clin Invest* 11:917 1932
- Williams M H Zohman L R and Ritner A C Hemodynamic effects of cardiac glycosides on normal human subjects during rest and exercise *J Appl Physiol* 13:417 1958
- Dock W and Hunter M L The circulatory changes after full therapeutic doses of digitalis with a critical discussion of views on cardiac output *J Clin Invest* 8:467 1930
- Katz L N Rodbard S Friend M and Rottersman W The effect of digitalis on the anesthetized dog I Action on the splanchnic bed *J Pharmacol Exp Ther* 62:11 1938
- Nadler J L Berger A R and Ballinger J Action of ouabain on the splanchnic circulation in the dog *J Lab Clin Med* 24:557 1940
- Cotten M DeV and Stopp P L Action of digitalis on the nonfailing dog heart *Am J Physiol* 192:114 1958
- Ross J Braunwald E and Waldhausen J A Studies on digitalis II Extracardiac effects on venous return and on the capacity of the peripheral vascular bed *J Clin Invest* 39:937 1960
- Harrison L A Blaschke J Phillips R S Price W E Cotten M DeV and Jacobson E D Effects of ouabain on the splanchnic circulation, *J Pharmacol Exp Ther* 169:1371 1969
- Selzer A Hultgren H N Ebner C L Bradley H W and Stone A O Effect of digoxin on the circulation of normal man *Br Heart J* 21:335 1959
- Dresdale D T Luccoglu V 7 Michtom R J Schultz M and Langer M Effects of furosemide C on cardiovascular hemodynamics Acute digitalizing doses in subjects with normal hearts and with heart disease without failure *Am J Cardiol* 1:88 1959
- Kux M and Massion W H Effects of L-coli organisms on hemodynamics of the dog lung *Ann Surg* 173:116 1971
- Steel R G D and Torrie J H Principles and procedures of statistics New York 1960 McGraw Hill Book Co Inc
- Ireat L Uchino H B and Jacobson L D Effects of intrarterial ouabain on mesenteric and carotid hemodynamics *J Pharmacol Exp Ther* 179:144 1971
- Uchino H B Ireat E Chiang A C K Jacobson L D Splanchnic circulatory responses to ouabain in shock *Surgery* 70:678 1971
- Shanbour L I Jacobson E D Brobman G I and Hershaw I B Effects of ouabain on splanchnic hemodynamics in the rhesus monkey *Am Heart J* 81:511 1971

VAGI INTACT

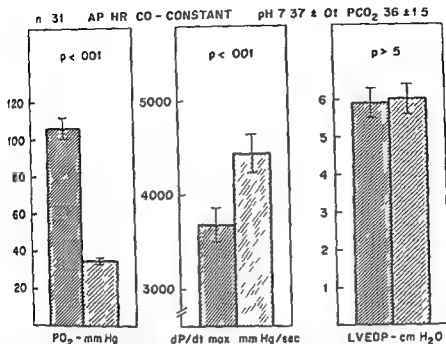


Fig. 3. Relationship of arterial oxygen tension (P_{O_2}) to dP/dt max and left ventricular end diastolic pressure (LVEDP) with constant aortic pressure (AP), heart rate (HR) and cardiac output (CO). Average values of 31 responses in 10 animals. Vertical brackets indicate standard error of mean. Vagi and adrenal glands intact.

pressure was controlled by an adjustable constant pressure reservoir.

Arterial pH, P_{O_2} and PCO_2 were continuously measured with a Jewett flow through electrode assembly and were frequently checked with an Instrumentation Laboratories system. Blood temperature was continuously maintained at $37 \pm 1^\circ C$ by passage through a Sarns heat exchanger. Cardiac frequency was held constant by electrical pacing of the left atrium. Bilateral carotid body denervation was carried out by sectioning Hering's nerves in selected experiments. Aortic body chemoreceptor denervation was achieved by performing bilateral mid cervical vagotomy.¹⁰ Desired levels of hypoxia were produced by substituting nitrogen for oxygen in the respiratory gas mixture using a gas mixing device.¹²

Changes in ventricular contractility were assessed from the maximal rate of change of left ventricular pressure (dP/dt max)¹⁴ for a given left ventricular end-diastolic pressure (LVEDP) while cardiac output, aortic pressure and heart rate were maintained constant. The rate of change of left ventricular pressure (dP/dt) was obtained

with an unfiltered RC differentiating circuit with a time constant of 0.263 msec. This circuit has a frequency response of 100 Hz and a linear phase shift with frequency. All animals were given atropine (1 mg) intravenously and changes in left ventricular contractility were compared before and following aortic body chemoreceptor denervation before and after bilateral adrenalectomy and following beta adrenergic blockade with either propranolol or practolol. The completeness of beta blockade was confirmed with a test bolus of 0.1 μg of isoproterenol intravenously. The data were recorded on a Sinobern 358 direct writing recorder. For statistical evaluation of the results the mean values, standard errors of the mean and Student's *t* test values were calculated according to standard methods.¹ The differences were considered significant when the *P* value was less than 5 per cent.

Results

Cardiac responses to acute hypoxia with vagi intact. Ventricular responses to 31 episodes of hypoxia in 10 atropinized animals

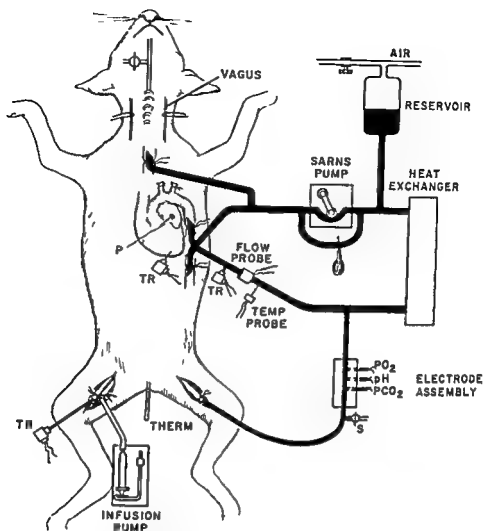


Fig. 1 Schematic representation of preparation used for measurement of ventricular performance under controlled hemodynamic conditions. Left ventricular output was measured with a cannulating type Medicon electromagnetic flow transducer. Pressures were measured in the aortic arch, left ventricle and femoral artery with Sanborn transducers (TR). Cardiac output was controlled with a Sarns roller pump after clamping of the temporary bypass. The pump was set to deliver a constant volume flow approximately equal to that measured prior to clamping of the bypass. Arterial pressure was held constant with a pressurized blood reservoir. Blood sample (S) were obtained at frequent intervals for confirmation of blood gas composition and pH. Temperature was controlled with a Sarns heat exchanger in conjunction with a Haake water bath and measured with a Yellow Springs probe in the aortic line and also with a rectal thermometer. P = pace electrode.

externalized through the abdominal wall. Interruption of the left adrenal circulation was performed by tightening the ligature after the animal was assured reflexic to both systemic hypoxia and temporary central nervous system (CNS) ischemia.¹¹ Postmortem examination confirmed the adequacy of ligation in all animals.

Respiration was controlled with a Harvard positive pressure pump and a midline thoracotomy was performed. Carbon dioxide was added to the respiratory gas mixture to maintain arterial PCO_2 near 35 mm Hg. Heparin (5 mg per kilogram of body weight) was given intravenously. The de-

scending aorta was cannulated and left ventricular output (minus coronary flow) was measured with a Statham cannulating type electromagnetic flow transducer and a Medicon K 2000 flowmeter (Fig. 1). Both the left subclavian and the brachiocephalic arteries were ligated and the latter was immediately cannulated with a branch from the aortic loop. Systemic blood flow was controlled with a Sarns roller pump after clamping the temporary bypass (Fig. 1). Sanborn transducers connected to 15 gauge 12½ inch stainless steel needles were utilized to measure pressures in the left ventricular chamber and aortic arch. Aortic

VAGOTOMY

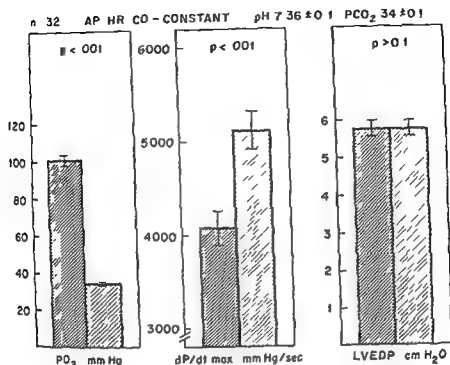


Fig. 4 Average changes of dP/dt max and end-diastolic pressure (LVEDP) during systemic hypoxia in 9 rats (32 pairs of studies) following bilateral mid-cervical vagotomy. Adrenal glands intact. Vertical brackets show standard error of mean.

bilaterally. Following right adrenalectomy but with the left adrenal intact arterial hypoxia (PO₂ 35 mm Hg) was associated with an increase of dP/dt max from 2340 to 2930 mm Hg per second and there was a small reduction in LVEDP. Following anareligation of the left adrenal vasculature re-exposure to hypoxia (PO₂ 25 mm Hg) was associated with comparable inotropic changes. After bilateral mid-cervical vagotomy the increases of dP/dt max in this animal were somewhat less (approximately 460 mm Hg per second) during hypoxia. These responses may be compared to temporary cephalic ischemia produced by interruption of brachiocephalic artery blood flow in which the increase of dP/dt max was approximately 1700 mm Hg per second. Following beta receptor blockade with practolol the positive responses to both hypoxemia and cephalic ischemia were virtually eliminated (less than 10 per cent) even though the initial fiber length increased during hypoxia as reflected by the elevation of LVEDP from 5 to 8 cm H₂O.

The data from all of the animals are summarized and compared in Fig. 6 before and following vagotomy, and before and following elimination of the adrenal component. When considered in terms of per cent increase of ventricular dP/dt max during acute hypoxemia (mean PO₂ 36 ± 1.3 mm Hg) the mean increment was 22 per cent in animals with intact adrenals and vagi and this increment was not changed by vagotomy (Fig. 6 top left panel). In animals without adrenals the increase of dP/dt max with acute hypoxia was 20.2 (± 3.6 SEM) per cent before vagotomy. Following vagal sectioning the mean increment was somewhat less (15.3 ± 1.5 SEM per cent) but this difference was not statistically significant.

In order to determine if the presence or absence of functioning adrenal glands modified the responses the data were further analyzed by comparing responses before and after adrenal removal in animals before vagotomy and after vagotomy (Fig. 6 lower panels). With the vagi intact

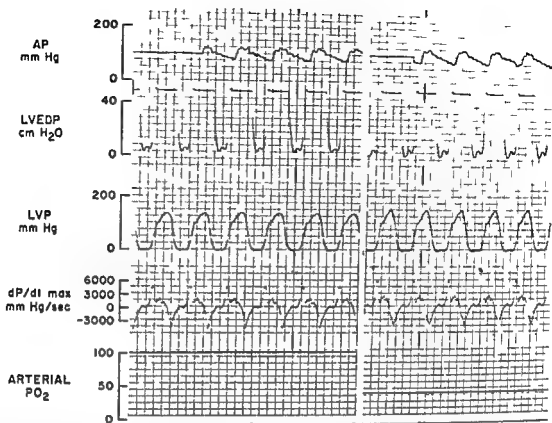


Fig 3 Original records following bilateral cervical vagotomy showing tracings with normal oxygenation (left panel) and during hypoxemia (right panel). With constant mean aortic pressure (AP) and heart rate (HR) end diastolic pressure (LVEDP) fell and dP/dt max increased during hypoxia. LVP = Left ventricular pressure. Chart speed = 100 mm per second. Adrenals intact.

with aortic chemoreceptors intact are summarized in Fig 2. The mean arterial pH during these experiments was $7.37 (\pm 0.01 \text{ SEM})$ and the mean PCO_2 was $36.4 (\pm 1.5 \text{ SEM})$ mm Hg. There was an average fall in PaO_2 from $106 (\pm 5 \text{ SEM})$ to $35 (\pm 2.5 \text{ SEM})$ mm Hg during ventilation with the hypoxic gas mixture. This was associated with a concomitant average increase in dP/dt max from $3,675$ to $4,438$ mm Hg per second, an increase of 763 mm Hg per second ($p < 0.001$). The average LVEDP remained unchanged at approximately 6 cm H_2O (Fig 2, right panel).

Cardiac responses to acute hypoxia following bilateral vagotomy. Representative tracings from an animal following vagotomy are shown in Fig 3. The aortic pressure and heart rate were held constant. When the arterial PO_2 was reduced from 100 to 38 mm Hg (Fig 3, right panel) the dP/dt max increased from $4,463$ to $5,950$ mm Hg per second, and the LVEDP fell from 4.5 to 3 cm H_2O . Responses to 32 episodes of hypoxia in 9 animals following vagotomy

are summarized in Fig 4. With an average reduction in arterial PO_2 from 102 to 34 mm Hg, there was a mean increase in dP/dt max from $4,088$ to $5,018$ mm Hg per second, an increase of 930 mm Hg per second ($p < 0.001$). The average arterial pH was 7.36 and PCO_2 was 34 mm Hg. The mean LVEDP remained unchanged at 5.8 cm H_2O (Fig 4, right panel).

In none of the animals was the response attenuated or abolished by the vagotomy procedure. Similar findings were observed in two cats with prior bilateral carotid sinus and body denervation.

Inotropic responses to acute hypoxia following adrenalectomy. In order to test the possibility that the ventricular responses during acute hypoxia were consequent to either reflex or direct release of catecholamines from the adrenal medulla into the circulation, the adrenal glands in six animals were excised or devascularized as described above. The results from a representative experiment are shown in Fig 5. The carotid sinus region was denervated

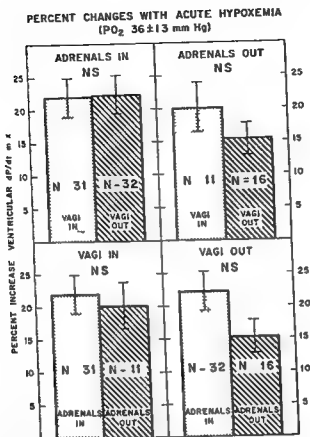


Fig 6 Mean incremental changes of left ventricular dP/dt max before and following adrenalectomy and before and following vagotomy. Vertical brackets indicate standard error of the mean. The values were assessed for statistical significance using a standard unpaired and unequal sample t test.

ity and the end-diastolic pressure. It has been shown that dP/dt max is one of the most sensitive measures which indicate changes in force-velocity relations in the intact heart.^{16,17} Under carefully controlled hemodynamic conditions with heart rate, cardiac output and aortic pressure held constant, this measurement faithfully reflects acute changes in the inotropic state of the myocardium. Evidence that this is valid in the present study is found in the data from animals following beta adrenergic blockade (summarized in Fig 7). There was no change of dP/dt max during exposure to hypoxemia in animals with or without adrenal function following the administration of either propranolol or practolol. Thus it is unlikely that the responses observed prior to beta blockade in the same preparations can be ascribed to mechanical or hemodynamic changes or to other modes

of cardiac stimulation such as changes in serum ion concentrations.

There is general agreement that most or all of the afferent fibers from the aortic chemoreceptors reach the medullary centers by way of the vagus nerves.¹⁰ Hence it is likely that most of the sensory input from these structures would be interrupted by bilateral mid cervical vagotomy. The principal objective of this study was to determine the effects of interruption of these fibers on the sympathetic outflow to the myocardium during hypoxia. Parasympathetic function was eliminated by atropine administration. This obviated the problem of possible changes in ventricular contractility that might result from interruption of efferent vagal discharge following the vagotomy procedures.¹⁸

The results of these experiments have failed to demonstrate a contribution from

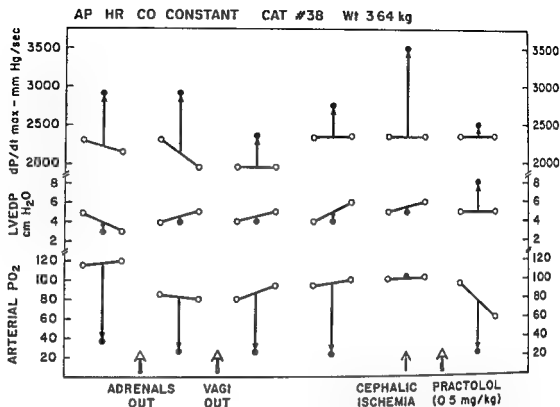


Fig 5 Sequential measurements of left ventricular performance with normal oxygenation (open circles) and during hypoxemia (closed circles). See text for description of procedures.

(Fig 6 lower left panel) the average increment of 22.2 per cent did not differ from the 20.2 per cent increase in animals with out adrenal glands. In the vagotomized preparations (Fig 6 lower right panel) there was a somewhat greater difference in the mean per cent increase (22.3 per cent with the adrenals in and 15.3 per cent with the adrenals out). Although these differences suggest a contribution from the adrenal glands in the vagotomized animals they did not prove to be statistically significant.

Left ventricular responses to hypoxemia following beta adrenergic blockade in seven animals with adrenals intact and in six with bilateral ablation of adrenal function are summarized in Fig 7. The average dP/dt max with full oxygenation in animals with intact adrenals was approximately 3700 mm Hg per second. The increase with hypoxemia observed prior to blockade was completely abolished. The average value for LVEDP increased from 7 to 7.5 cm H₂O during hypoxia, but this difference was not significant. Those animals subjected to early removal of adrenal function had a substantially lower dP/dt max with

full oxygenation (2200 mm Hg per second). Beta blockade completely abolished the increase observed prior to blockade. In this group there was a small but significant ($p < 0.01$) increase of end diastolic pressure from 6.5 to 8.2 cm H₂O during exposure to hypoxia. Thus the positive inotropic responses observed in both groups of animals were abolished following beta adrenergic blockade.

Discussion

The findings in the present study are consistent with earlier conclusions that during acute hypoxemia adrenergic stimulation of the myocardium is importantly enhanced in the intact mammal.¹ A primary objective was to explore the mode of transduction of the hypoxic stimulus with major emphasis on the aortic chemoreceptor system. A second objective was to determine if there was an important contribution from the adrenal glands by reflex or direct release of catecholamines into the circulation.

Changes of ventricular contractility were assessed from changes in the maximal rate of pressure rise in the left ventricular cavity.

who were able to demonstrate in the mature fetal lamb that stimulation of the carotid chemoreceptors with sodium cyanide elicited cardiovascular responses that could not be reproduced with hypoxemia. They concluded that the difference may be a function of the intensity of the stimulus.

While there appears to be a dichotomy in the response pattern of the two peripheral chemoreceptor groups in that the carotid group may diminish cardiac sympathetic outflow^{1,2} while aortic chemoreceptor stimulation may enhance it³ the majority of evidence supports the view that the peripheral chemoreceptors are not the only and probably not the most important sensory system responsible for modulation of sympathetic outflow to the heart during hypoxia. A more important source is suggested by the observations of Alexander⁴ and of Gelhorn, Cortell and Carlson.²² These investigators showed that alterations of blood gas composition within the central nervous system may directly stimulate autonomic centers in the hypothalamus, medulla and spinal cord.

It is well known that reduced blood flow to the central nervous system elicits an increase of heart rate, myocardial contractility and peripheral vascular resistance in the adult²³ and in the newborn.²⁴ This was also demonstrated in the present study and is illustrated in Fig. 5. Baroreceptors have not been identified in the cephalic vessels. This suggests the possibility that the chronotropic and inotropic responses may be related to development of hypoxia and hypercapnia of the autonomic centers when these are deprived of adequate blood flow. It also suggests that these structures may be sensitive to alterations of arterial PO_2 and PCO_2 even in the presence of normal blood flow. This hypothesis has been shown to be correct.^{25,26} It appears most likely therefore that the sensory system primarily responsible for enhanced sympathetic outflow to the heart during hypoxia as well as hypercapnia resides within the central nervous system and represents an intrinsic functional property of the autonomic centers. The recent work of Krasney²⁷ suggests that these centers may also be sensitive to histotoxic hypoxia produced by cyanide administration. This provides further evidence to support the concept of

central chemosensitivity in cardiovascular autonomic regulation.¹⁴

Summary

The sensory system responsible for increased ventricular contractility (VC) during hypoxemia is not fully established. Previous studies have demonstrated that isolated carotid body hypoxia is not associated with an increase of VC.⁸ However, reflexly increased VC may result from pharmacologic stimulation of the aortic chemoreceptors.⁹ In order to evaluate their contribution during hypoxia, VC was studied in atropinized cats before and following denervation by bilateral vagotomy. VC was measured under conditions of constant aortic pressure, cardiac output and heart rate. Arterial blood gases and pH were continuously monitored. With hypoxemia (PO_2 27 to 46 mm Hg) all cats showed an increase of VC manifested by an increase of dP/dt for a given end-diastolic pressure. The responses were unaltered by bilateral vagotomy. Similar findings were obtained in animals with bilateral carotid body denervation. The increase of VC during hypoxia was not significantly less following adrenalectomy. Beta adrenergic blockade completely abolished these responses. It is concluded that the increase in VC associated with systemic hypoxia cannot be entirely attributed to aortic or carotid chemoreceptor reflex activity. The influence of stimulation of structures within the central nervous system must also be considered.

The technical assistance of Mr. Ronald Gordon and Mr. Victor Hardaswick is gratefully acknowledged.

REFERENCES

1. Cross C E, Reiben P A, Barron C I and Salisbury F F. Effects of arterial hypoxia on the heart and circulation. An integrative study. *Am J Physiol* 203: 963, 1963.
2. Downing S E. Autonomic influences on cardiac function in systemic hypoxia. In Hatcher J D and Jennings D B, editors. International symposium on cardiovascular and respiratory effects of hypoxia—Kingston, Ontario, New York, 1965. S. Karger, Basel, p. 208.
3. Downing S E, Gardner T H and Rocaamore J M. Adrenergic support of cardiac function during hypoxia in the newborn lamb. *Am J Physiol* 211: 728, 1969.
4. Kahler R L, Goldblatt A and Braunwald E. The effects of acute hypoxia on the systemic

RESPONSES TO HYPOXEMIA AFTER BETA BLOCKADE

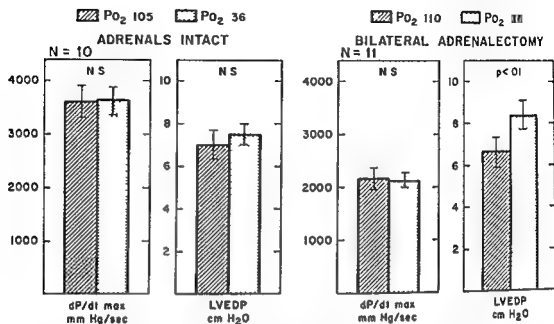


Fig 7 Left ventricular responses to hypoxemia following beta adrenergic blockade in animals with intact adrenal glands (left panels) and following bilateral adrenalectomy (right panels). Vertical brackets indicate standard error of the mean. Positive inotropic responses were completely abolished. In the adrenalectomized animals there was a small but significant increase of end diastolic pressure (LVEDP) during hypoxia ($p < 0.01$).

hypoxic stimulation of the aortic chemoreceptors to the recorded increments of dP/dt max. With the afferent fibers intact, reduction of the arterial PO_2 to 35 mm Hg was associated with a $22.2 (\pm 2.9 \text{ SEM})$ per cent increase of dP/dt max. Following bilateral vagotomy the same level of hypoxemia induced a $22.3 (\pm 3.0 \text{ SEM})$ per cent increase. These findings are consistent with earlier electrocardiographic observations⁷ which demonstrated large increments of impulse traffic in the inferior cardiac branch of the stellate ganglion during exposure to acute hypoxia. Equally large increments were observed following bilateral sectioning of the vagi and Hering's nerves. These findings therefore do not support the concept that stimulation of peripheral chemoreceptors is essential to modulation of sympathetic outflow to the heart in systemic hypoxia.

The adrenal glands provide another potential source for adrenergic stimulation of the myocardium through the release of increased amounts of catecholamine into the circulation. It is unlikely, however, that sufficient norepinephrine could be obtained from this source to provide detectable changes in ventricular performance during acute hypoxia.¹⁸ This idea is consistent with

present findings in which the increment of dP/dt max was $20.2 (\pm 3.6 \text{ SEM})$ per cent following removal of adrenal function compared with an increment of $22.2 (\pm 2.9 \text{ SEM})$ per cent with adrenal function intact ($p > 0.8$). The effect of adrenalectomy appeared to be somewhat greater in the vagotomized animals in that the increase of dP/dt max was $15.3 (\pm 2.5 \text{ SEM})$ per cent but this difference did not prove to be statistically significant (Fig 6, lower right panel). It is more likely that the lower average value is attributable to the additional surgical manipulations incident to the adrenalectomy procedures.

The work of Stern and Rapaport⁹ has shown that chemical stimulation of receptors in the region of the aortic arch can reflexly increase cardiac contractility and that the afferent limb of the reflex arch is carried in the vagus nerves. The present studies do not preclude the possibility that hypoxic stimulation of aortic chemoreceptor tissue may contribute to the positive inotropic responses seen in systemic hypoxia. It does seem clear, however, that the cardiac responses are undiminished in the absence of afferent input from this source.¹⁹ Thus a parallel may be drawn with the observations of Dawes and associates²¹

External left atrial pulse tracings in extreme left atrial dilation

Nabil El Sherif M D

Zaki El Ramly M D

Cairo Egypt U A R

Considering the frequency of rheumatic disease of the mitral valve extreme left atrial dilation is a rare condition. The enlarged chamber may easily be mistaken for right pleural effusion with the potential hazard of aspiration.^{1,2} Clinical recognition is not easy and sometimes thoracotomy has been performed to establish the diagnosis.³ Patients with extreme left atrial dilation present with a rather characteristic spectrum of physical signs of which the presence of systolic pulsations of the right anterior chest wall attributed to the left atrium is considered the most characteristic. The present report deals with the recording of these pulsations which form a valuable diagnostic tool.

Case reports

Case 1 A 34 year old woman was first seen in April 1967 because of moderate limitation of effort tolerance. There was a history suggestive of rheumatic fever at the age of 9 with recurrent attacks of arthritis for the next few years. When the patient was 12 years old a cardiac murmur was heard and a tonsillectomy was performed. Attacks of paroxysmal nocturnal dyspnea occurred infrequently and severe hemoptysis occurred once. A stitchlike chest pain, localized to the right axilla but frequently referred to the right shoulder began one year prior to admission. It subsided a few months later. The

patient mentioned a slight dysphagia on swallowing but said that it caused her little trouble.

On examination the patient was found to be slightly underdeveloped and in no apparent distress. The jugular venous pulse was elevated 2 to 3 cm. above the sternal angle there was atrial fibrillation and the blood pressure was 130/80 mm Hg. The liver was enlarged two fingerbreadths below the right costal margin and there was slight ankle edema. Chest examination revealed a small thoracic cage and a marked precordial bulge.

Cardiologic examination showed a heaving apical impulse in the seventh space in the anterior axillary line and a palpable third heart sound. There was a moderate parasternal heave. Systolic expansion of the right anterior thoracic wall was both visible and palpable. Cardiac dullness extended to the right anterior axillary line and there was dullness on the lower right lung base. Auscultation revealed a holosystolic murmur Grade 4/6 over the apex with a loud third heart sound and a short mid-diastolic murmur. The systolic murmur was wide spread and could be heard clearly on the right side and on both lung bases. The electrocardiogram (ECG) showed coarse fibrillatory waves, right axis deviation and high voltage of the M waves in the left surface leads. A chest roentgenogram revealed a greatly enlarged cardiac shadow that touched the chest wall on both the left and right sides (Fig. 1). There were lines of old pleural reaction on the right side. The esophagus was displaced posteriorly and to the left with marked angulation in the left lateral view (Fig. 2). Fluoroscopy showed vague pulsations of the right cardiac border.

With the patient in the supine position the right

From the Cardiology Department, Faculty of Medicine, Cairo University, Egypt U A R.

Received for publication April 18, 1971.

Reprint requests to Dr. Nabil El Sherif, Cardiology Department, Faculty of Medicine, Cairo University, Cairo, Egypt U A R.

- venous and arterial systems and on myocardial contractile force *J Clin Invest* 41:1553 1962
- 5 Nahas G G Mather G W Wingo J D M and Adams W I Influence of acute hypoxia on sympathetomized and adrenalectomized dogs *Am J Physiol* 177:13 1954
 - 6 DeGeest H Levy M N and Zieske H Carotid chemoreceptor stimulation and ventricular performance *Am J Physiol* 209:564 1965
 - 7 Downing S L and Siegel J H Baroreceptor and chemoreceptor influences on sympathetic discharge to heart *Am J Physiol* 204:471 1963
 - 8 Downing S E Remensnyder J P and Mitchell J H Cardiovascular responses to hypoxic stimulation of the carotid bodies *Circ Res* 10:676 1962
 - 9 Stern E and Rappaport E Comparison of the reflexes elicited from combined or separate stimulation of the aortic and carotid chemoreceptors on myocardial contractility cardiac output and systemic resistance *Circ Res* 20:214 1967
 - 10 Comroe J H The location and function of the chemoreceptors of the aorta *Am J Physiol* 127:176 1939
 - 11 Achtel R A and Downing S E Adrenergic influences on ventricular performance during hypoxemia before and following peripheral chemoreceptor denervation *Fed Proc* 29:720 1970
 - 12 Downing S L and Gardner T H Reflex regulation of ventricular work performance *Yale J Biol Med* 39:173 1966
 - 13 Grand M G and Downing S E Metabolic and reflex influences on pulmonary vasomotion *Am J Physiol* 218:654 1970
 - 14 Downing S E Mitchell J H and Wallace A G Cardiovascular responses to ischemia hypoxia and hypercapnia of the central nervous system *Am J Physiol* 204:881 1963
 - 15 Lewis A L Biostatistics New York 1966 Reinhold Publishing Co p 60
 - 16 Hood W H Jr Covelli V H Abelmann W H and Norman J C Persistence of contractile behaviour in acutely ischaemic myocardium *Cardiovasc Res* 3:749 1969
 - 17 Reeves T J Hefner L L Jones W B Coghlan C Prieto G and Carroll J Hemodynamic determinants of the rate of change in pressure in the left ventricle during isometric contraction *Am HEART J* 60:745 1960
 - 18 Levy M N Martin P Ng M and Zieske H Sympathetic and parasympathetic interactions upon the left ventricle of the dog *Circ Res* 19:5 1969
 - 19 Toyooka C T and Blake W D Effect of hypoxia on sympathoadrenal activity in dogs with myocardial insufficiency *Am J Physiol* 201:448 1961
 - 20 Krasney J A Cardiovascular responses to cyanide in awake sinoaortic denervated dogs *Am J Physiol* 220:1361 1971
 - 21 Dawes G S Duncan S L B Lewis B V Merlet C L Owen Thomas J B and Koeves J T Cyanide stimulation of the systemic arterial chemoreceptors in foetal lambs *J Physiol (Lond)* 201:117 1969
 - 22 Alexander R S The effects of blood flow and anoxia on spinal cardiovascular centers *Am J Physiol* 113:698 1945
 - 23 Gellhorn E Cortell R and Carlson H H Fundamental differences in the excitability of somatic and autonomic centers in response to anoxia *Am J Physiol* 133:641 1941
 - 24 Downing S E Gardner T H and Solis R T Autonomic influences on cardiac function in the newborn lamb *Circ Res* 19:947 1966
 - 25 DeGeest H Levy M N and Zieske H Reflex effects of cephalic hypoxia hypercapnia and ischemia upon ventricular contractility *Circ Res* 17:349 1965



Fig 1 Chest radiograph P A view of first case

anterior thoracic pulsations were recorded from the fourth intercostal space in the anterior axillary line with the use of a pick up bell secured in place by a rubber strap simultaneously with the left ventricular apexcardiogram (ACG) and the phonocardiogram (PCG) at the mitral area. The recordings were made on a four channel Mingograph type 42B at a paper speed of 50 mm per second (Fig 3). The tracing revealed a pulse wave contour typical of left atrial pulse tracings in the presence of mitral regurgitation. There was a positive CV wave with a rapid Y descent. The C wave was synchronous with the high pitched components of the first heart sound in the PCG and corresponded to a notch on the ascending limb of the left ventricular ACG. The A wave showed a rapid decline to a point (a) marking the annular ascent point.⁴ This point was synchronous with the third heart sound.

Venous catheterization revealed a moderately elevated wedge pressure. The pulmonary artery pressure and the pulmonary arteriolar resistance were only slightly above normal limits (Fig 4 and Table I). A diagnosis of dominant mitral regurgitation with extreme left atrial dilation was made and the patient was discharged on maintenance doses of digitalis and diuretic therapy.

The patient was readmitted in December 1968 with dyspnea and right embolic hemiparesis and was given anticoagulants. The dyspnea rapidly regressed but the motor power showed only slight improvement. On the eighteenth day following admission the patient suffered a sudden attack of severe dyspnea with frothy blood tinged sputum. Drowsiness and hypotension soon followed and the patient died two hours later.

Postmortem examination revealed an enormously enlarged heart that almost filled the entire chest. The main chamber was the left atrium which was markedly dilated and contained more than 2 l of blood. It showed close contact with the right thoracic wall especially on the anterior and lateral



Fig 2 Chest radiograph left lateral view of first case

aspects. The wall was thin and fibrous and was no more than 1 mm thick. The endocardium showed calcification especially prominent in the auricular appendage but there was no mural thrombosis. The right atrium was about one third the size of the left with the endocardium showing patchy calcification and hypertrophied pectinate muscles. The left ventricle was markedly dilated and hypertrophied and measured 15 cm in thickness the right ventricle also dilated measured 0.5 cm. The mitral valve was heavily calcified showing severe regurgitation with slight stenosis at the commissures the circumference measured 35 mm. Microscopic examination of the left atrium showed marked fibrosis of the wall with very few muscle fibers and scattered Aschoff bodies.

Case 2 A 35 year old man was admitted to the hospital in January 1969 complaining of dyspnea on moderate exertion frequent attacks of paroxysmal nocturnal dyspnea and a persistent cough with broncho pasm. He had had rheumatic arthritis at the age of 13 and it had recurred several times in subsequent years.

Examination revealed a well nourished man in no apparent distress. The jugular venous pulse was slightly raised. Atrial fibrillation was detected in the pulse and the blood pressure was 130/85 mm Hg. The liver was enlarged one fingerbreadth below the right costal margin and there was slight edema around the ankles. The chest was small with a moderate precordial bulge.

Cardiologic examination showed a heaving apical impulse in the sixth space in the anterior axillary line with a loud palpable third heart sound followed by a short diastolic thrill. Systolic pulsations were evident on the right anterior thoracic wall and were

early of the mitral valve to the aortic point which was synchronous with the peak of the RFW of the left ventricular ACG and the third heart sound in the ECG. Immediately following the aortic point the left atrial pulse tracing showed a rapid rise marking the wave of diastasis that continued until the next C wave.

Venous catheterization revealed a moderately raised wedge pressure. The pulmonary artery pressure and the pulmonary arteriolar resistance were fully bone normal (Table 1). The patient was found to have severe mitral regurgitation with extreme left atrial dilation and was advised to have a mitral valve replacement but she refused the operation and was later discharged on maintenance doses of digitalis and an oral diuretic.

In October 1970 the patient three months pregnant, was admitted for a medically induced abortion. Although the operation was completed uneventfully the patient developed severe bleeding 12 hours later with marked hypotension. Resuscitation failed.

On postmortem examination the heart was found to occupy no less than 80 per cent of the thoracic cavity with marked compression of both lungs. The main cardiac chamber was the left atrium which occupied the entire right hemithorax in close contact with the thoracic cage on the anterior, lateral and posterior aspects. The left atrium was dilated contained 78 L of blood and had a fibrous wall no more than 1 mm thick. The right atrium was moderately dilated and contained multiple post mortem thrombi. The left ventricle was hypertrophied and dilated and its wall was 13 mm thick. The wall of the right ventricle was 5 mm thick. The mitral valve showed marked fibrotic deformity the free margins of the cusps were rolled rigid and calcified. The circumference of the valve was 43 mm or $3\frac{1}{2}$ times the normal. Microscopic examination of the left atrium showed marked fibrosis of the wall with almost complete replacement of the muscle fibres.

Discussion

This report presents for the first time external recordings of right thoracic pulsations in three patients with rheumatic mitral regurgitation and extreme left atrial dilation. The pulsations were attributed to the fact that the enormously dilated left atrium was in close contact with the right thoracic wall. This study was conducted following an earlier observation of marked pulsation of the right anterior thoracic wall in a patient with rheumatic mitral regurgitation and extreme left atrial dilation. In this case, external tracings were not recorded. The patient died following a massive pulmonary embolism and postmortem examination showed the markedly dilated left atrium coming in close contact with the right thoracic wall for a considerable area



Fig. 7 Chest radiograph P A view of third case

In the following three years three more cases were discovered.

These patients present with a rather characteristic spectrum of physical signs that can frequently establish the diagnosis. The minimal evidence of congestive failure when first seen the consistent finding of atrial fibrillation the displaced and heaving apical impulse dominant mitral regurgitation and the wide spread of the systolic murmur to both lung bases and to the right anterior thoracic wall were common findings in our cases. Most characteristic among the physical signs is the extension of the cardiac dullness to the right of the sternum frequently as far as the axillary line with both visible and palpable pulsations in these areas. This dullness together with the dullness at the right posterior lung base have led to the erroneous diagnosis of right pleural effusion in some cases.² The dullness and pulsations are attributed to the dilated left atrium. This rightward extension of left atrial dullness is explained by the anatomy of this chamber where the line of least resistance for left atrial dilation is rightward with both anterior and posterior extensions.^{2,3}

In contrast to the characteristic physical signs the symptomatology is not usually diagnostic. In fact some of the previously mentioned characteristic symptoms such as right sided chest pain have received various descriptions and explanations from

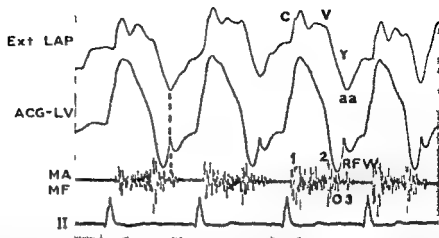


Fig. 6 Case 2 External left atrial pulse tracing (Ext LAP) recorded simultaneously with left ventricular atrial cardiological (ACG LV) and PEG at the mitral area 1 2 and 3 First second and third heart sounds C V and Y left atrial c and v waves and y descent aa annular ascent point O stands for both the O point of the ACG LV and the opening snap of the PEG RFIW rapid filling wave MF mitral area MF medium frequency

The pulmonary artery pressure was slightly elevated and the cardiac output was diminished (Table I). In a later attempt the left ventricle was approached percutaneously from the right femoral artery entry into the left atrium was attempted but failed. The patient was maintained on digitalis and diuretic therapy and showed marked response. In August 1969 the patient died shortly after a non cardiac surgery. A postmortem report mentioned that the left atrium was extremely enlarged extending into the right hemithorax and coming in close contact with a considerable area of the right anterior thoracic wall. The right atrium was moderately dilated. The walls of the right and left ventricles were 5 and 12 mm thick respectively. The mitral valve was markedly regurgitant with an opening of $3\frac{1}{2}$ finger breadths.

Case 3 A 27 year old woman was first seen in September 1969 complaining of moderate limitation of effort tolerance occasional attacks of paroxysmal nocturnal dyspnea mild orthopnea and recurrent chest infection with bronchospasm. She had had her first attack of rheumatic arthritis at the age of 9 years and since then she had experienced several other attacks. A cardiac murmur was first discovered at the age of 11 and soon afterward the cardiac symptoms began. The patient was married at the age of 18 and her first pregnancy and labor took place at the age of 20 with little discomfort. Congestive failure developed during the third trimester of her second and third pregnancies at ages 22 and 25 respectively. The congestive failure progressed rapidly after labor and the patient had been irregularly receiving antifailure therapy for the 2 years preceding this admission.

Examination revealed a well nourished woman in no apparent distress. The jugular venous pulse was raised 2 to 3 cm above the sternal angle. Atrial fibrillation was detected in the pulse the blood pressure was 120/80 mm Hg bilaterally. The liver was palpable one fingerbreadth below the right costal margin there was no ankle edema. Chest exami-

nation revealed a thoracic cage of moderate size with an evident precordial bulge.

Cardiologic examination showed a heaving apical impulse displaced to the seventh space in the anterior axillary line with a palpable third heart sound. There was a moderate parasternal heave. Systolic pulsations were both seen and felt on the right anterior axillary and lower posterior thoracic wall with clear systolic expansion of the anterior part of the right hemithorax. The cardiac dullness extended to the whole right hemithorax on the anterior axillary and lower posterior sides. Auscultation revealed a holosystolic murmur Grade 4/6 on the apex with a loud third heart sound and a short mid diastolic rumble. The systolic murmur was widespread and could be clearly heard on the whole right side of the chest. The ECG showed coarse fibrillatory waves right axis deviation and a moderate degree of clockwise rotation in the precordial leads. The chest roentgenogram revealed a greatly enlarged cardiac shadow that touched the chest wall on both the left and right sides (Fig. 7). The left lateral view showed displacement of the esophagus posteriorly and to the left with marked angulation.

Fig. 8 illustrates the simultaneous recording of cardiac pulsations from a point at the fifth space in the right midaxillary line (the external left atrial pulse tracing) and a point at the seventh space in the left anterior axillary line (the left ventricular ACG) together with the ECG at the mitral area. The tracing obtained from the right thoracic wall revealed a pulse wave contour typical of left atrial pulse tracings in the presence of mitral regurgitation. The curve consisted of a positive C wave with a rapid Y descent. The C wave was synchronous with the high pitched components of the first heart sound from the V peak the curve declined in the Y descent which consisted of three phases. The first phase was a decline which extended from the peak of the Y wave to the O point of the left ventricular ACG which marked the opening of the mitral valve. The second phase was a rapid fall from the time of the

gurgitation may show not only freely pulsating neck veins and a pulsating liver but also a massive pulsation of the right side of the chest that yields almost square waves which may superficially simulate those demonstrated in the present study. However the question of differentiating the right thoracic pulsations in patients with extreme left atrial dilation does not seem to be a major problem in many of these cases: there is slight or no evidence of tricuspid regurgitation when first seen. In our four patients with extreme left atrial dilation evidence of significant tricuspid regurgitation was uniformly absent on the first examination when the right thoracic pulsations were initially detected. The jugular venous pulse was slightly raised and the liver was only one or two finger breadths enlarged. Hemodynamic studies in all cases showed consistently normal end-diastolic pressure of the right ventricle and normal right atrial pressure (Table I and Fig. 4). The finding of right thoracic pulsations in a patient with severe mitral regurgitation but with minimal evidence of tricuspid regurgitation should immediately raise the possibility of marked left atrial dilation.

Analysis and correlation of intracardiac left atrial pulse tracings in mitral valve disease with the underlying hemodynamic disturbances and with events in the cardiac cycle and the PCG have been frequently reported.⁸⁻¹⁰ This work, however, gives the first description of such correlation using an external left atrial pulse tracing and proves that the external tracing reflects the same qualitative changes in the left atrial pressure although it lacks the quantitative value. The external left atrial pulse tracing will aid in determining which type of mitral valve lesion is present. Although dominant mitral regurgitation is the most frequent underlying factor and therefore the external left atrial pulse tracing will be consistent with this hemodynamic disturbance yet in the uncommon instances in which dominant mitral stenosis is present the external left atrial pulse tracing will prove characteristic. Observation of our difficulty in advancing the catheter to a wedge position in the second case and the failure of our attempt to enter the left atrium because of the marked change in the anatomic rela-

tionship will make the external left atrial pulse tracing most valuable in some of the cases.

The external recording of direct left or right atrial pulsations has not been previously reported. In a recent study of the left parasternal pulsations as represented by the right ventricular ACG in cases of rheumatic tricuspid stenosis we found a prominent presystolic a wave which was not observed in the right ventricular pressure pulse. The size of the a wave was found to correlate fairly well with the calculated tricuspid valve area. Since the wave could not be explained as a result of the right atrial contraction causing the blood to enter the ventricle leading to change in the right ventricular end-diastolic volume (as in the case of pulmonary hypertension for example) it was feasible to consider it representative of direct right atrial tracing as sensed by the recording piece applied at the left sternal border.¹¹

Extreme left atrial dilation with right thoracic pulsations is a rare condition. In the last three years we have found only four cases among the 120 patients with dominant mitral regurgitation admitted during that period (3.3 per cent). No patient with mitral regurgitation with moderate left atrial dilation showed right thoracic pulsations which is consistent with the anatomic considerations of the disease. On the other hand, none of the 242 patients with mitral stenosis seen in the same period showed extreme left atrial dilation or right thoracic pulsations. Most of those reported to have extreme left atrial dilation had mitral regurgitation³ however on rare occasions mitral stenosis may be associated with rather large atria.¹²

The presence of systolic pulsations of the right anterior thoracic wall was reported infrequently in the early cases of extreme left atrial dilation. In a later publication Sloan and associates⁸ stressed its diagnostic value in their three patients with massive dilation of the left atrium. Although De Sanctis, Dern and Bland² reported the pulsations in only one of their ten patients with extreme left atrial dilation yet in two others there were systolic pulsations of the right posterolateral chest wall. The relatively infrequent reporting of these pulsations may be ascribed to variations in a

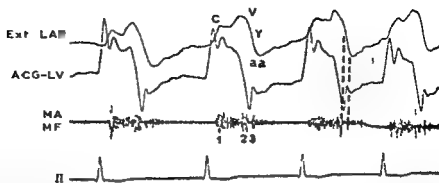


Fig 8 Case 3 External left atrial pulse tracing (Ext L1P) recorded simultaneously with left ventricular apex cardiogram (ICG LV) and PCG at the mitral area 1, 2 and 3 First second and third heart sound C V and Y left atrial c and v waves and y descent aa annular ascent point M1 mitral area MF medium frequency

Table I Hemodynamic data in three cases of extreme left atrial dilation

Case No	Wedge (mm Hg)	PA* (mm Hg)	RV (mm Hg)	RA (mm Hg)	CO (L/min)	PA R (dynes sec cm ⁻²)
1	22/13(17)	32/11(21)	32/0	3/0	3.2	100
2	—	38/18(26)	38/3	4/1	4.2	—
3	23/12(16)	34/15(22)	34/2	5/2	3.5	137

*PA = pulmonary artery, RV = right ventricle, RA = right atrium, CO = cardiac output and PA R = pulmonary arteriolar resistance

quently with little rationale^{2,3} The right sided chest pain of our patient was thought to be pleuritic in origin. On the other hand mild dysphagia was discovered in one patient and only by means of direct questioning. The rarity of embolization previously mentioned² contrasts with its presence both in our early case of extreme left atrial dilation and in the first case in this report although in the former case the embolization was right sided and only in the second case can we implicate the enlarged left atrium. However there was no evidence of mural thrombosis at postmortem examination. The only characteristic feature of these patients may be the observed discrepancy between the fair degree of effort tolerance and the degree of cardiac enlargement attributed mainly to the left atrial dilation.

The recording over the right thoracic wall of a pulse wave contour consistent with left atrial pulse tracing is not an unexpected finding in view of the anatomic considerations of the disease. In our four cases with

extreme left atrial dilation, the enormously dilated atrium was shown in postmortem examination to have close contact with a wide area of the right thoracic wall. In the three patients in whom external tracings were obtained the recording piece was applied to an area of the right thoracic wall that was later shown to have close contact with the left atrial chamber. An important indication that we are dealing with genuine left atrial pulse tracings is provided by analysis of the contour of the curve and its timing which are characteristic in relation to the left ventricular hemodynamic events as represented by the left ventricular ACG and the auscultatory phenomena as revealed by the PCG at the mitral area.

Although it may be questioned whether we are dealing with a true pressure curve or a volume curve it is probable that in the markedly dilated left atrium the pressure and the volume rise and fall together.

It may be argued that right thoracic pulsations are caused by tricuspid regurgitation. Patients with severe tricuspid re-

Postural hypotension in amyloid disease

D Gaan MRCP MRCPE*

M P Mahoney MRCP

D J Rowlands MRCP

Aled W Jones D Path

Manchester England

Postural hypotension may occur during the course of primary amyloidosis^{1,2} usually in association with other signs and symptoms of autonomic dysfunction and peripheral neuropathy. It has been assumed to be due to autonomic involvement but it has never been investigated and its pathophysiological mechanism has not been established.

In this report we describe a patient with primary amyloidosis who presented with the nephrotic syndrome and subsequently developed incapacitating postural hypotension. He had no other manifestations of autonomic disturbance and no clinical evidence of peripheral neuropathy. Hemodynamic studies were performed and the results correlated with the pathological findings.

Case report

A 61-year-old man was admitted to the Department of Medicine, Manchester Royal Infirmary in November 1961. For ten months he had complained of general ill health, loss of appetite, excessive tiredness, and progressive swelling of the legs. He had had no effort and moderate dyspnea on exertion for the last two years. His past and family history were noncontributory.

On examination he looked pale and had extensive edema of the legs and sacral region. The pulse was 82 beats per minute and regular, the blood pressure was 110/80 mm Hg, the heart sound

were normal and there was no elevation of the jugular venous pressure. Examination of the respiratory system and abdomen yielded negative results. No abnormality was detected in the nervous system in particular the tendon jerks were brisk and symmetrical and there was no superficial or proprioceptive sensory impairment. There was no detectable thickening of peripheral nerves.

Laboratory investigations The hemoglobin was 15.7 Gm per 100 ml, the white blood cell count was 11,400 per cubic millimeter, the erythrocyte sedimentation rate was 10 mm in 1 hour (Wintrobe), the platelet count was 242,000 per cubic millimeter, the reticulocyte count was 2 per cent.

The urinary protein excretion in 24 hours was 13 Gm, the serum albumin was 1.9 Gm per 100 ml, the serum globulin was 1.8 Gm per 100 ml, electrophoresis showed a slight increase in the alpha₂ globulins with marked reduction of the gamma globulins, the blood urea was 25 mEq per 100 ml, the serum electrolytes were within normal limits (serum cholesterol 330 mg per 100 ml, serum calcium 8.6 mg per 100 ml, serum inorganic phosphorus 4.7 Gm per 100 ml, serum creatinine 1.0 mg per 100 ml, urea clearance 49 ml per minute, creatinine clearance 120 ml per minute).

Examination of the urine revealed 50 pus cells per high power field and a growth of *Escherichia coli*; this infection responded to ampicillin and did not recur. An intravenous pyelogram did not reveal any abnormality.

The antistreptolysin O titer was less than 50 Todd units, results of the lupus erythematosus test, antinuclear factor, sensitized sheep cell and F II latex tests were repeatedly negative.

The glucose tolerance test result was normal and the Wasserman Reaction was negative.

From the Department of Medicine, Manchester Royal Infirmary, Manchester, England.

Received for publication May 12, 1971.

Revised for publication June 15, 1971.

Revised for publication July 15, 1971.

Revised for publication August 15, 1971.

Revised for publication September 15, 1971.

Revised for publication October 15, 1971.

Revised for publication November 15, 1971.

Revised for publication December 15, 1971.

Revised for publication January 15, 1972.

Revised for publication February 15, 1972.

Revised for publication March 15, 1972.

Revised for publication April 15, 1972.

Revised for publication May 15, 1972.

Revised for publication June 15, 1972.

Revised for publication July 15, 1972.

Revised for publication August 15, 1972.

Revised for publication September 15, 1972.

Revised for publication October 15, 1972.

Revised for publication November 15, 1972.

Revised for publication December 15, 1972.

Revised for publication January 15, 1973.

Revised for publication February 15, 1973.

Revised for publication March 15, 1973.

Revised for publication April 15, 1973.

Revised for publication May 15, 1973.

Revised for publication June 15, 1973.

Revised for publication July 15, 1973.

Revised for publication August 15, 1973.

Revised for publication September 15, 1973.

Revised for publication October 15, 1973.

Revised for publication November 15, 1973.

Revised for publication December 15, 1973.

Revised for publication January 15, 1974.

Revised for publication February 15, 1974.

Revised for publication March 15, 1974.

Revised for publication April 15, 1974.

Revised for publication May 15, 1974.

Revised for publication June 15, 1974.

Revised for publication July 15, 1974.

Revised for publication August 15, 1974.

Revised for publication September 15, 1974.

Revised for publication October 15, 1974.

Revised for publication November 15, 1974.

Revised for publication December 15, 1974.

Revised for publication January 15, 1975.

Revised for publication February 15, 1975.

Revised for publication March 15, 1975.

Revised for publication April 15, 1975.

Revised for publication May 15, 1975.

Revised for publication June 15, 1975.

Revised for publication July 15, 1975.

Revised for publication August 15, 1975.

Revised for publication September 15, 1975.

Revised for publication October 15, 1975.

Revised for publication November 15, 1975.

Revised for publication December 15, 1975.

Revised for publication January 15, 1976.

Revised for publication February 15, 1976.

Revised for publication March 15, 1976.

Revised for publication April 15, 1976.

Revised for publication May 15, 1976.

Revised for publication June 15, 1976.

Revised for publication July 15, 1976.

Revised for publication August 15, 1976.

Revised for publication September 15, 1976.

Revised for publication October 15, 1976.

Revised for publication November 15, 1976.

Revised for publication December 15, 1976.

Revised for publication January 15, 1977.

Revised for publication February 15, 1977.

Revised for publication March 15, 1977.

Revised for publication April 15, 1977.

Revised for publication May 15, 1977.

Revised for publication June 15, 1977.

Revised for publication July 15, 1977.

Revised for publication August 15, 1977.

Revised for publication September 15, 1977.

Revised for publication October 15, 1977.

Revised for publication November 15, 1977.

Revised for publication December 15, 1977.

Revised for publication January 15, 1978.

Revised for publication February 15, 1978.

Revised for publication March 15, 1978.

Revised for publication April 15, 1978.

Revised for publication May 15, 1978.

Revised for publication June 15, 1978.

Revised for publication July 15, 1978.

Revised for publication August 15, 1978.

Revised for publication September 15, 1978.

Revised for publication October 15, 1978.

Revised for publication November 15, 1978.

Revised for publication December 15, 1978.

Revised for publication January 15, 1979.

Revised for publication February 15, 1979.

Revised for publication March 15, 1979.

Revised for publication April 15, 1979.

Revised for publication May 15, 1979.

Revised for publication June 15, 1979.

Revised for publication July 15, 1979.

Revised for publication August 15, 1979.

Revised for publication September 15, 1979.

Revised for publication October 15, 1979.

Revised for publication November 15, 1979.

Revised for publication December 15, 1979.

Revised for publication January 15, 1980.

Revised for publication February 15, 1980.

Revised for publication March 15, 1980.

Revised for publication April 15, 1980.

Revised for publication May 15, 1980.

Revised for publication June 15, 1980.

Revised for publication July 15, 1980.

Revised for publication August 15, 1980.

Revised for publication September 15, 1980.

Revised for publication October 15, 1980.

Revised for publication November 15, 1980.

Revised for publication December 15, 1980.

Revised for publication January 15, 1981.

Revised for publication February 15, 1981.

Revised for publication March 15, 1981.

Revised for publication April 15, 1981.

Revised for publication May 15, 1981.

Revised for publication June 15, 1981.

Revised for publication July 15, 1981.

Revised for publication August 15, 1981.

Revised for publication September 15, 1981.

Revised for publication October 15, 1981.

Revised for publication November 15, 1981.

Revised for publication December 15, 1981.

Revised for publication January 15, 1982.

Revised for publication February 15, 1982.

Revised for publication March 15, 1982.

Revised for publication April 15, 1982.

Revised for publication May 15, 1982.

Revised for publication June 15, 1982.

Revised for publication July 15, 1982.

Revised for publication August 15, 1982.

Revised for publication September 15, 1982.

Revised for publication October 15, 1982.

Revised for publication November 15, 1982.

Revised for publication December 15, 1982.

Revised for publication January 15, 1983.

Revised for publication February 15, 1983.

Revised for publication March 15, 1983.

Revised for publication April 15, 1983.

Revised for publication May 15, 1983.

Revised for publication June 15, 1983.

Revised for publication July 15, 1983.

Revised for publication August 15, 1983.

Revised for publication September 15, 1983.

Revised for publication October 15, 1983.

Revised for publication November 15, 1983.

Revised for publication December 15, 1983.

Revised for publication January 15, 1984.

Revised for publication February 15, 1984.

Revised for publication March 15, 1984.

Revised for publication April 15, 1984.

Revised for publication May 15, 1984.

Revised for publication June 15, 1984.

Revised for publication July 15, 1984.

Revised for publication August 15, 1984.

Revised for publication September 15, 1984.

Revised for publication October 15, 1984.

Revised for publication November 15, 1984.

Revised for publication December 15, 1984.

Revised for publication January 15, 1985.

Revised for publication February 15, 1985.

Revised for publication March 15, 1985.

Revised for publication April 15, 1985.

Revised for publication May 15, 1985.

Revised for publication June 15, 1985.

Revised for publication July 15, 1985.

Revised for publication August 15, 1985.

Revised for publication September 15, 1985.

Revised for publication October 15, 1985.

Revised for publication November 15, 1985.

Revised for publication December 15, 1985.

Revised for publication January 15, 1986.

Revised for publication February 15, 1986.

Revised for publication March 15, 1986.

Revised for publication April 15, 1986.

Revised for publication May 15, 1986.

Revised for publication June 15, 1986.

Revised for publication July 15, 1986.

Revised for publication August 15, 1986.

Revised for publication September 15, 1986.

Revised for publication October 15, 1986.

Revised for publication November 15, 1986.

Revised for publication December 15, 1986.

Revised for publication January 15, 1987.

Revised for publication February 15, 1987.

Revised for publication March 15, 1987.

Revised for publication April 15, 1987.

Revised for publication May 15, 1987.

Revised for publication June 15, 1987.

Revised for publication July 15, 1987.

Revised for publication August 15, 1987.

Revised for publication September 15, 1987.

Revised for publication October 15, 1987.

Revised for publication November 15, 1987.

Revised for publication December 15, 1987.

Revised for publication January 15, 1988.

Revised for publication February 15, 1988.

Revised for publication March 15, 1988.

Revised for publication April 15, 1988.

Revised for publication May 15, 1988.

Revised for publication June 15, 1988.

Revised for publication July 15, 1988.

Revised for publication August 15, 1988.

Revised for publication September 15, 1988.

Revised for publication October 15, 1988.

Revised for publication November 15, 1988.

Revised for publication December 15, 1988.

Revised for publication January 15, 1989.

Revised for publication February 15, 1989.

Revised for publication March 15, 1989.

Revised for publication April 15, 1989.

Revised for publication May 15, 1989.

Revised for publication June 15, 1989.

Revised for publication July 15, 1989.

Revised for publication August 15, 1989.

Revised for publication September 15, 1989.

Revised for publication October 15, 1989.

Revised for publication November 15, 1989.

Revised for publication December 15, 1989.

Revised for publication January 15, 1990.

number of parameters including, in particular, the degree of left atrial dilation and its anatomic characteristics especially the degree of extension in the anterior direction in relation to the size and anatomy of the thoracic cage. Our first two patients had small thoracic cages.

The recording of external left atrial pulse tracings of classical mitral regurgitation in patients with extreme left atrial dilation may prove that the distensibility and pressure characteristics of a markedly dilated left atrium do not differ to any appreciable degree from those of the moderately dilated left atrium commonly encountered. This distensibility enables the markedly dilated left atrium to "absorb" both the large ventricular regurgitant jet and the raised diastolic pressure of a failed ventricle and in a way, to protect the pulmonary vascular bed from the effect of raised pressure. Our finding of slightly elevated pulmonary artery pressure and normal pulmonary arteriolar resistance favors this hypothesis.

Summary

In three cases of extreme left atrial dilation in patients with rheumatic mitral regurgitation while the symptomatology was nonspecific the clinical examination offered a rather characteristic spectrum of physical signs most significant of which was the presence of systolic pulsations of the right anterior thoracic wall attributed to the dilated left atrium. The recording of these pulsations showed a pulse wave contour exactly similar to the intracardiac left atrial pulse tracing in mitral regurgitation.

It is suggested that the tracing can help in the diagnosis of both extreme left atrial dilation and of the nature of the underlying mitral valve disease.

REFERENCES

- 1 Owen I O and Fenton W J. A case of extreme dilation of the left auricle of the heart. *Clin Soc Trans* 34 183 1901
- 2 De Sanctis R W, Dein D C and Blind L F. Extreme left atrial enlargement. Some characteristic features. *Circulation* 29 14 1964
- 3 Sloan S, Pollock R C, Kirschbaum J and Reedman T. Massive dilation of the left auricle. Report of three cases. *Ann Intern Med* 40 75 1954
- 4 Ridner S. Left atrial pulse curve. Significance of annular recent wing. *Acta Med Scand* 159 219 1957
- 5 Daley K and Frank R. Massive dilation of the left auricle. *Quart J Med* 18 81 1949
- 6 Morrow A G, Braunwald E, Haller J A and Sharp E H. Left atrial pressure pulse in mitral valve disease. A correlation of pressures obtained by transbronchial puncture with the valvular lesion. *Circulation* 16 399 1957
- 7 Nixon P G F, Wooler G H and Radigan I K. The opening snap in mitral incompetence. *Br Heart J* 22 395 1960
- 8 Nixon P G F. Time relationships of the left atrial V wave in mitral valvular disease. *Br Heart J* 23 637 1961
- 9 Nixon P G F. The third heart sound in mitral regurgitation. *Br Heart J* 23 677 1961
- 10 Nixon P G F and Wooler G H. The S of diastole in mitral valvular disease. *Br Heart J* 25 393 1963
- 11 El Sherif N. Rheumatic tricuspid stenosis. A haemodynamic correlation. *Br Heart J* 33 16 1971
- 12 Kent E M, Fisher D L, Ford W B and Neville J F Jr. Mitral valve surgery and left heart catheterization in giant left atrium. *Arch Surg* 73 503 1956

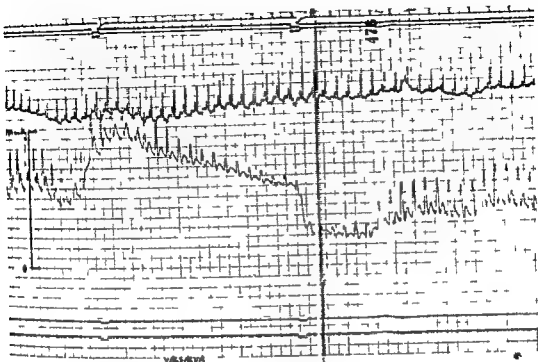


Fig. 2 The ECG (upper tracing) and intra-arterial pressure record (lower tracing) during Valsalva maneuver. The pressure scale is shown on the left. The time marker at the top of the tracing gives 1 sec intervals.

Table 1 Hemodynamic findings

Heart rate (per min.)	Cardiac output (L/min)	Blood pressure (mm Hg)			Right atrial pressure (mm Hg)	Peripheral resistance (units)
		Systolic	Diastolic	Mean		
Lying						
96	2.2	84	54	62	3	28
96	2.2					
96	2.3					
96	2.3					
96	2.2					
Standing						
95	2.0	55	41	46	—	23

Hemodynamic investigations The heart rate, arterial pressure, central venous pressure and cardiac output were measured. The heart rate was determined from a continuous recording of the ECG (using the Seldinger technique a 55 cm. piece of FG4 (Portex Ltd) tubing was inserted percutaneously into the right brachial artery and advanced under x-ray screening control to the aortic root. This tube was used to measure central arterial pressure and to withdraw arterial blood for cardiac output determinations. A similar piece of FG4 tubing was inserted percutaneously into the right antecubital vein and advanced into the right atrium to measure

the central venous pressure and to inject dye for cardiac output determination. Pressures were measured with a P23Gb Statham transducer using a Sanborn carrier amplifier and a Mingograph 81 (Elema) Recorder. The cardiac output was determined by the dye dilution technique using the Waters 301 densitometer and cuvette and a Gilford withdrawal pump.

Measurements were taken with the subject lying down and standing and the subject performed Valsalva maneuver while lying. The results are shown in Table 1 and Fig. 2.

The cardiac output was low in the presence of a

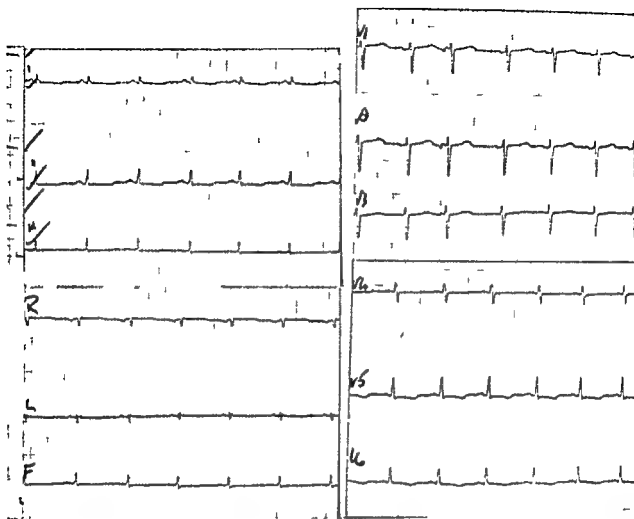


Fig 1 The patient's ECG

A chest x ray revealed small healed tuberculous foci at the left apex; the rest of the lung fields was clear and the cardiac shadow was normal. The electrocardiogram (ECG) showed small QRS complexes and flattening or inversion of T waves in most leads (Fig 1).

The prothrombin time of a control subject was 12.5 seconds; that of the patient was 17 seconds. This prolongation of the prothrombin time was further investigated and was found to be due to a mild factor VII deficiency and did not respond to intramuscular injections of vitamin K₁.

The serum bilirubin, thymol turbidity, alkaline phosphatase, serum glutamic oxalacetic transaminase, and serum glutamic pyruvic transaminase were within normal limits.

A bromsulphthalein test showed 40 per cent retention at 30 minutes and 25 per cent retention at 45 minutes. A renal biopsy contained about 36 glomeruli; the majority of which showed no abnormality. A few glomeruli revealed small focal deposits of amorphous material in the mesangial stalk, which gave a faintly positive reaction with Congo red. The arteries, tubules, and interstitium showed no abnormality. A rectal biopsy did not reveal evidence of amyloid disease.

Treatment and progress The patient was treated

with bed rest, a high protein-low salt diet, and diuretic therapy without any significant response. A short course of prednisolone given at another hospital during the early course of the disease had been without effect. He was discharged from the hospital in December of 1967.

A few weeks later he attended the outpatient clinic complaining of postural dizziness and fainting attacks and was found to have marked postural hypotension with a blood pressure of 110/0 mm Hg lying down and 75/0 standing. He was readmitted on February 15, 1968. Apart from the severe postural hypotension, the physical signs were as noted on his previous admission. There were no signs of cardiac failure and repeated examination of the nervous system was negative. An autonomic neuropathy was suspected, and this view was supported by the results of the hemodynamic studies. The postural symptoms became so severe that the patient was unable to sit or stand. He developed an infected necrotic ulcer on the lower lip which was complicated by septicemia with β hemolytic streptococci to which the patient succumbed despite treatment on March 10, 1968. His blood urea remained normal throughout the course of his illness until a few days prior to his death, when it rose to a maximum level of 60 mg per 100 ml.

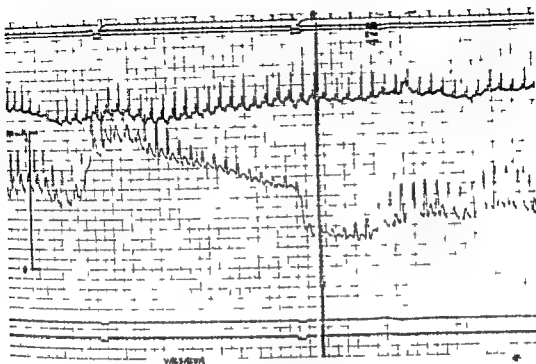


Fig 2 The ECG (upper traces) and intra-arterial pressure record (lower traces) during Valsalva's maneuver. The pressure scale is shown on the left. The time marker at the top of the traces gives 1 sec intervals.

Table 1 Hemodynamic findings

Heart rate (per min)	Cardiac output (L/min)	Blood pressure (mm Hg)			Right atrial pressure (mm Hg)	Peripheral resistance (units)
		Systolic	Diastolic	Mean		
Lying						
96	2.2	84	54	62	3	28
96	2.2					
96	2.3					
96	2.3					
96	2.2					
Standing						
96	2.0	55	41	46	—	23

Hemodynamic investigations. The heart rate, arterial pressure, central venous pressure, and cardiac output were measured. The heart rate was determined from a continuous recording of the ECG using the Seldin technique. A 55 cm. piece of FG4 (Portex Ltd.) tubing was inserted percutaneously into the right brachial artery and advanced under x-ray screening control to the aortic root. This tube was used to measure central arterial pressure and to withdraw arterial blood for cardiac output determinations. A similar piece of FG4 tubing was inserted percutaneously into the right antecubital vein and advanced into the right atrium to measure

the central venous pressure and to inject dye for cardiac output determination. Pressures were measured with a P23Gb Statham transducer using a Sanborn carrier amplifier and a Mingograph 81 (Elema) Recorder. The cardiac output was determined by the dye dilution technique using the Waters K 301 densitometer and cuvette and a Gilford withdrawal pump.

Measurements were taken with the subject lying down and standing and the subject performed Valsalva's maneuver while lying. The results are shown in Table 1 and Fig 2.

The cardiac output was low in the presence of a

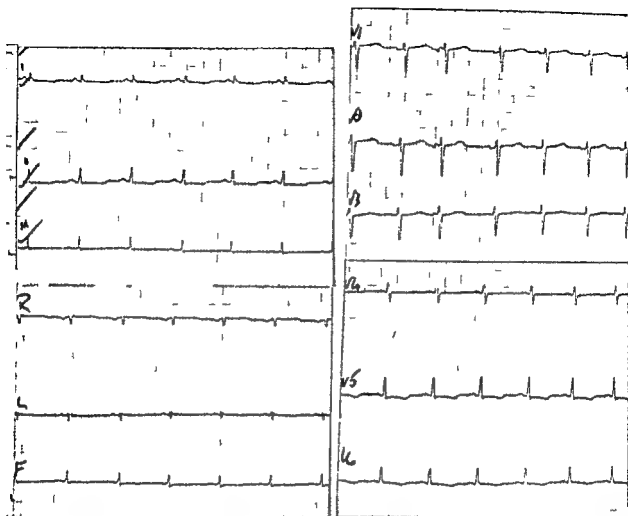


Fig 1 The patient's ECG

A chest x ray revealed small healed tuberculous foci at the left apex, the rest of the lung fields was clear and the cardiac shadow was normal. The electrocardiogram (ECG) showed small QRS complexes and flattening or inversion of T waves in most leads (Fig 1).

The prothrombin time of a control subject was 12.5 seconds; that of the patient was 17 seconds. This prolongation of the prothrombin time was further investigated and was found to be due to a mild factor VII deficiency and did not respond to intramuscular injections of vitamin K₁.

The serum bilirubin, thymol turbidity, alkaline phosphatase, serum glutamic oxalacetic transaminase, and serum glutamic pyruvic transaminase were within normal limits.

A bromsulphthalein test showed 40 per cent retention at 30 minutes and 25 per cent retention at 45 minutes. A renal biopsy contained about 36 glomeruli, the majority of which showed no abnormality. A few glomeruli revealed small focal deposits of amorphous material in the mesangial stalk which gave a faintly positive reaction with Congo red. The arteries, tubules, and interstitium showed no abnormality. A rectal biopsy did not reveal evidence of amyloid disease.

Treatment and progress The patient was treated

with bed rest, a high protein-low salt diet, and diuretic therapy without any significant response. A short course of prednisolone, given at another hospital during the early course of the disease, had been without effect. He was discharged from the hospital in December of 1967.

A few weeks later he attended the outpatient clinic complaining of postural dizziness and fainting attacks and was found to have marked postural hypotension with a blood pressure of 110/70 mm Hg lying down and 75/0 standing. He was readmitted on February 15, 1968. Apart from the severe postural hypotension, the physical signs were as noted on his previous admission. There were no signs of cardiac failure and repeated examination of the nervous system was negative. An autonomic neuropathy was suspected, and this view was supported by the results of the hemodynamic studies. The postural symptoms became so severe that the patient was unable to sit or stand. He developed an infected necrotic ulcer on the lower lip which was complicated by septicemia with β hemolytic streptococci to which the patient succumbed despite treatment on March 10, 1968. His blood urea remained normal throughout the course of his illness until a few days prior to his death when it rose to a maximum level of 60 mg per 100 ml.

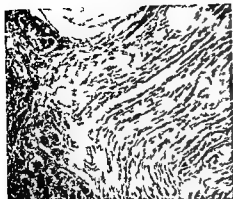


Fig 3 Part of a thoracic sympathetic ganglion with an afferent branch showing infiltration with amyloid (Hematoxylin and eosin $\times 480$)

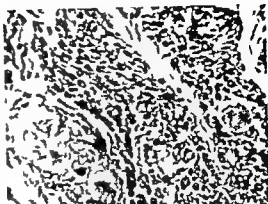


Fig 4 A lumbar nerve trunk containing amyloid deposits. (Hematoxylin and eosin $\times 380$)

154 published cases⁸ diarrhea was present in 13 per cent and neurological involvement in 13.6 per cent.

Postural hypotension in amyloid disease has never been investigated hemodynamically; it has been presumed to be due to autonomic neuropathy but in some cases has been ascribed to myocardial involvement. In our patient postural hypotension was the only manifestation of autonomic involvement and this occurrence in the absence of any clinical signs of peripheral neuropathy has been reported only once previously.⁹ The severity of the hypotension was responsible for the giddiness and fainting attacks. Mild or moderate degrees of orthostatic hypotension may however be present without producing any symptoms and this sign which may be the only manifestation of autonomic neuropathy may be missed unless especially looked for.

The place of the Valsalva maneuver in demonstrating autonomic dysfunction as a cause of orthostatic hypotension is now well established.^{10, 11} In healthy subjects the acute rise in intrathoracic pressure impedes venous return and produces a fall in stroke volume and pulse pressure and ultimately a decrease in the systolic and diastolic pressures. This stimulates baroreceptors in the carotid sinus and aortic arch leading to reflex vasoconstriction which stops any further drop in the blood pressure and persists after release of the intrathoracic pressure leading to an overshoot of the blood pressure above the original level and to reflex bradycardia. These

responses are absent in patients with autonomic neuropathy and were not observed in our patient. The absence of any alteration in the pulse rate on standing and during and after the Valsalva maneuver is evidence of impairment of the positive and negative chronotropic nervous drive to the heart and it is likely that the fixed heart rate (96 per minute) represents the intrinsic rate of the sinoatrial node. This patient thus showed evidence of central and peripheral autonomic cardiovascular denervation.

The cause of the amyloid neuropathy was originally ascribed to metabolic factors¹² or to ischemic degeneration secondary to vascular involvement by amyloid substance.^{7, 13, 17} However pathological studies have clearly demonstrated as in the present case that amyloid deposition is usually extensive involving nerve bundles and ganglion cells as well as the epineural and perineural vessels^{14, 15, 18, 19} and it is now believed that the neuropathy is mainly due to direct compression of neural structures by the amyloid material. The extensive demyelination of nerves found in the present case is probably a nonspecific response of nerve fibers to amyloid deposits.

Postural hypotension is a physical sign which is not frequently looked for unless severe enough to produce symptoms. Its presence has been noted in most cases of primary amyloidosis with signs of peripheral polyneuropathy which constituted 13.6 per cent in one series⁸; it is possible that mild or moderate degrees of ortho-

Table II Anatomical distribution of amyloid and extent of its deposition

Organ involved	Tissue	Vessels
Spleen	+++++	+
Heart	+++++	+
Adrenals	+++++	+
Kidney	++	++
Lip (ulcer)	++	+
Tongue	+	-
Thyroid	+	+
Lung	+	+
Seminal vesicles	=	++
Prostate	=	++
Pancreas	+	-
Liver	-	++
Rectum	-	=
Spinal cord	-	-

normal filling pressure suggesting myocardial failure. On standing there was no increase in the peripheral resistance and the arterial pressure fell while the heart rate remained constant. There was a slight fall in the cardiac output presumably due to a decrease in venous return. During Valsalva maneuver the patient achieved an increase in the intrathoracic pressure of approximately 30 mm Hg. There was no increase in the heart rate during the procedure and no reflex bradycardia or overshoot of the arterial pressure after its termination.

The sum total of these findings was taken as evidence of central and peripheral cardiovascular denervation with some degree of myocardial involvement.

Autopsy findings

MACROSCOPIC FINDINGS: There was extensive edema of the legs and sacrum and a large necrotic ulcer at the mucocutaneous junction of the lower lip. Both pleural sacs contained serous effusions (right 500 ml, left 520 ml). The heart was enlarged and weighed 480 grams. The coronary arteries showed a severe degree of stenosing atheroma. The myocardium was pale and abnormally firm. In the lungs there was some degree of puckering and fibrosis at the left apex and four small pulmonary infarcts in the left lung, estimated to be between seven and ten days old with organizing thrombi in the corresponding branches of the pulmonary arteries. The peritoneal sac contained 1 200 ml of clear yellowish fluid. The liver was firm in consistency and weighed 1 520 grams. The gallbladder contained several small mixed stones. The spleen was slightly enlarged and weighed 280 grams. Its outstanding features were its extreme firmness and its homogenous waxy appearance on cut section. The kidneys did not show any macroscopic abnormality and the total kidney mass was 310 grams.

MICROSCOPIC FINDINGS: There was widespread deposition of amyloid material in almost all organs, the only exceptions being the brain, spinal cord and pituitary gland. The anatomical distribution and extent of deposition in the different organs is shown

Table III Amyloid distribution in left sympathetic chain

Site	Amount
Inferior cervical ganglion	+
Upper thoracic chain	++
Midthoracic ganglion	+++
Splanchnic nerve	+
Lower thoracic chain	+
Upper lumbar ganglion and chain	+
Lumbar ganglion	+

Table IV Amyloid distribution in the peripheral nervous system

	Nerve	Vessels	
		Epineural	Perineural
Lumbar nerve root	+++	+	+++
Sacral nerve root	+++	+	+++
Left median nerve	=	-	+
Cervical posterior root ganglion	++	NA	NA
Right and left median popliteal nerve	+	-	++

in Table II. The thoracic and lumbar segments of both sympathetic chains were examined with as many of the branches as possible. Extensive amyloid deposition was found throughout the sympathetic ganglia and nerves (Table III and Fig 3). All the peripheral nerves examined showed involvement by amyloid (Fig 4) and the findings are summarized in Table IV. The amyloid was deposited both within the nerve bundles and also in the interfascicular (epineural) and intrafascicular (perineural) vessels. The nerves showed extensive demyelination. Amyloid was also found in the small blood vessels and tissues at the base of the lip ulcer. The amyloid substance was identified by the different staining reactions and was examined by ordinary and electron microscopy.

Discussion

A review of previous reports of cases of primary amyloidosis reveals that when autonomic manifestations were present there were usually associated signs of peripheral polyneuropathy. The autonomic manifestations consisted in most cases of gastrointestinal symptoms, impotence or postural hypotension.^{1,2} In a review of

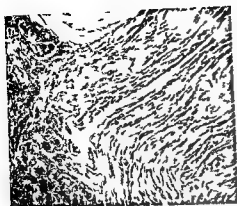


Fig 3 Part of a thoracic sympathetic ganglion with an efferent branch showing infiltration with amyloid (Hematoxylin and eosin $\times 480$)



Fig 4 A lumbar nerve trunk containing amyloid deposits (Hematoxylin and eosin $\times 350$)

154 published cases⁸ diarrhea was present in 13 per cent and neurological involvement in 13.6 per cent.

Postural hypotension in amyloid disease has never been investigated hemodynamically; it has been presumed to be due to autonomic neuropathy but in some cases has been ascribed to myocardial involvement. In our patient postural hypotension was the only manifestation of autonomic involvement and this occurrence in the absence of any clinical signs of peripheral neuropathy has been reported only once previously.² The severity of the hypotension was responsible for the giddiness and fainting attacks. Mild or moderate degrees of orthostatic hypotension may however be present without producing any symptoms and this sign which may be the only manifestation of autonomic neuropathy may be missed unless especially looked for.

The place of the Valsalva maneuver in demonstrating autonomic dysfunction as a cause of orthostatic hypotension is now well established.¹⁰⁻¹⁴ In healthy subjects the acute rise in intrathoracic pressure impedes venous return and produces a fall in stroke volume and pulse pressure and ultimately a decrease in the systolic and diastolic pressures. This stimulates baroreceptors in the carotid sinus and aortic arch leading to reflex vasoconstriction which stops any further drop in the blood pressure and persists after release of the intrathoracic pressure leading to an overshoot of the blood pressure above the original level and to reflex bradycardia. These

responses are absent in patients with autonomic neuropathy and were not observed in our patient. The absence of any alteration in the pulse rate on standing and during and after the Valsalva maneuver is evidence of impairment of the positive and negative chronotropic nervous drive to the heart and it is likely that the fixed heart rate (96 per minute) represents the intrinsic rate of the sinoatrial node. This patient thus showed evidence of central and peripheral autonomic cardiovascular denervation.

The cause of the amyloid neuropathy was originally ascribed to metabolic factors¹⁵ or to ischemic degeneration secondary to vascular involvement by amyloid substance.^{7,16,17} However pathological studies have clearly demonstrated as in the present case that amyloid deposition is usually extensive involving nerve bundles and ganglion cells as well as the epineural and perineural vessels^{8,9,15,18,19} and it is now believed that the neuropathy is mainly due to direct compression of neural structures by the amyloid material. The extensive demyelination of nerves found in the present case is probably a nonspecific response of nerve fibers to amyloid deposits.

Postural hypotension is a physical sign which is not frequently looked for unless severe enough to produce symptoms. Its presence has been noted in most cases of primary amyloidosis with signs of peripheral polyneuropathy which constituted 13.6 per cent in one series⁸; it is possible that mild or moderate degrees of ortho-

static hypotension are missed and this sign may be present in a much higher percentage of cases of primary amyloidosis even in the absence of other neurological signs, as in the present case. On the basis of this and other reported cases we suggest that this physical sign should be especially looked for in any patient suffering from an obscure neuropathy or the nephrotic syndrome, or suspected to be suffering from amyloid disease, if other more obvious causes of orthostatic hypotension such as diabetes mellitus, neurosyphilis, and hypovolemia are excluded the presence of significant postural hypotension in those cases should raise a strong suspicion of amyloid disease.

Summary

A patient with primary amyloidosis who developed severe postural hypotension during the course of the nephrotic syndrome is described. Hemodynamic studies demonstrated that this was due to autonomic dysfunction and revealed evidence of central and peripheral cardiovascular denervation. Pathological examination showed extensive infiltration of sympathetic ganglia and nerves with amyloid material. Postural hypotension was the only clinical evidence of neurological involvement in the absence of other manifestations of autonomic disturbance or signs of peripheral neuropathy.

We wish to express our thanks to Prof. D. A. K. Black for his permission to report this case and to Miss J. Barrett for her secretarial help.

REFERENCES

- 1 Fisher H and Preuss F S Primary systemic amyloidosis with involvement of the nervous system *Am J Clin Path* 21:758 1951
- 2 Wagner H N Orthostatic hypotension *Bull Johns Hopkins Hosp* 105:322 1959
- 3 Munstat T L and Foussaint A F Clinical manifestations and diagnosis of amyloid polyneuropathy. Report of three cases *Neurology* 12:413 1962
- 4 Liske E Chou S M and Thompson H G Jr Peripheral and autonomic neuropathy in amyloidosis. A case report *JAMA* 186:432 1963
- 5 French J M Hall G Parish D J and Smith W T Peripheral and autonomic nerve involvement in primary amyloidosis associated with uncontrollable diarrhea and steatorrhea *Am J Med* 39:277 1965
- 6 De Navasquez S, and Treble H A A case of primary generalized amyloid disease with involvement of the nerves *Brain* 61:116 1938
- 7 Keraohan J W and Wolfman H W Amyloid neuritis *Arch Neurol Psychiat* 47:132 1942
- 8 Rukavina J G Block W D Jackson C E Fall M F Carey J G, and Curtiss A Primary systemic amyloidosis. A review and an experimental genetic and clinical study of 29 cases with particular emphasis on the familial form *Medicine* 35:239 1956
- 9 Chambers R A Medd W E and Spencer H Primary amyloidosis with special reference to involvement of the nervous system *Quart Med J* 27:207 1958
- 10 McIntosh H D Burnum J F Hickam J B and Warren J V Circulatory changes produced by the Valsalva maneuver in normal subjects: patients with mitral stenosis and autonomic nervous system alterations *Circulation* 9:511 1954
- 11 Barany F R and Cooper E H Pilomotor and submotor innervation in diabetes *Clin Sci* 15:533 1956
- 12 Sharpey Schafer E P Circulatory reflexes in chronic disease of the afferent nervous system *J Physiol (London)* 134:1 1956
- 13 Sharpey Schafer E P and Taylor P J Absent circulatory reflexes in diabetic neuritis *Lancet* 1:559 1960
- 14 Watson W E Some circulatory responses to Valsalva's maneuver in patients with polyneuritis and spinal cord disease *J Neurol Neurosurg Psychiatry* 25:19 1962
- 15 Sullivan J F Twitchell T E Gherardi G J and Vanderhaan W P Amyloid polyneuropathy *Neurology* 5:847 1955
- 16 Gotz W and Krucke W Über Paramyloidose mit besonderer Beteiligung der peripheren Nerven und granularer Atrophie des Gehirns und über ihre Beziehungen zu den intracerebralen Gefäßerkrankungen *Arch Psychiatr Nervenkr* 114:183 1942
- 17 Strich S J and Wade G Primary amyloidosis presenting with peripheral neuritis and intractable heart failure *Lancet* 2:70 1953
- 18 Fudley J W Jr and Adams W Primary systemic amyloidosis simulating constrictive pericarditis with steatorrhea and hyperesthesia *Arch Intern Med* 81:342 1948
- 19 Clark R M and Bennett R F Peripheral nerve involvement in systemic primary amyloidosis *Lab Invest* 6:125 1957

Clinical pathologic conference

Robert V Schnitzler MD

Jules Cohen MD

Elliot O Lipchik MD

Eric A Schenk MD

Rochester NY

Case report

DR. ROBERT V. SCHNITZLER: A 51-year-old garage worker was admitted to Strong Memorial Hospital for the first time in December 1967 with a six-month history of increasing fatigue, cough, exertional and nocturnal dyspnea, and orthopnea. Six weeks prior to the admission he had been seen at his local hospital and a digitalis preparation and diuretics were begun. Despite a weight loss of ten pounds he developed ankle edema in addition to his other symptoms. There was no history of hypertension, thrombophlebitis or rheumatic fever.

Past history was pertinent in that two years prior to admission his physical examination had been negative. He was known to drink moderately and had smoked two to three packs of cigarettes daily for many years.

On physical examination his blood pressure was 110/60, pulse rate was 96 beats per minute and respirations were 18 per minute. The jugular venous pressure measured 4 cm. above the sternal angle and a prominent V wave was observed. Dullness and decreased breath sounds were present at the base of the left lung. The heart was markedly enlarged and the cardiac impulses suggested biventricular hypertrophy. The second sound was widely split and did not move with respiration. Pulmonary valve closure was markedly increased. A third heart sound was audible at the midclavicular line in the sixth intercostal space. A Grade 3/6 holosystolic murmur was heard at the left sternal border and at the apex. The liver was felt 4 cm. below the right costal margin and was tender to palpation. There was no clubbing of the fingers. Two-plus ankle edema was present.

The laboratory findings included a hematocrit of 40 per cent, a white blood count of 12,600 with 4 per cent polymorphonuclear cells, 1 per cent bands, 22 per cent lymphocytes, 2 per cent monocytes, and 1 per cent basophils. The peripheral

blood smear was normal. Corrected sedimentation rate was 22 mm per hour. Urinalysis was negative. Blood urea nitrogen, glucose, serum electrolytes, alkaline phosphatase, bilirubin, uric acid, creatinine, cholesterol, and glutamic oxalacetic transaminase were all within normal limits. Electrocardiographic (ECG) changes included some decrease in QRS voltage and T wave inversion in Leads I, aV₁, and V₄ (Fig 1). Marked cardiomegaly with left atrial enlargement was demonstrated on roentgenography of the chest (Fig 2). In addition, a left pleural effusion was present and the lungs appeared congested. Kerley B lines were seen.

Because the clinical diagnosis was uncertain, cardiac catheterization was performed. The results are summarized in Table I. On angiography a small left atrium was demonstrated. A mass was found compressing the chambers medially and inferiorly; no drainage could be demonstrated from the pulmonary veins of the left lower lobe of the lung. A filling defect also was noted partially occluding the pulmonary vein of the left upper lobe. Compression of the right pulmonary artery and displacement of the left pulmonary artery by a mediastinal mass were also demonstrated. These findings will be discussed in further detail.

Other laboratory data included a normal serum protein electrophoresis, six negative blood cultures, and Class I cells by sputum cytology. The patient improved over the next several days and was discharged with instructions to take digoxin. He had refused to undergo further studies.

In the ensuing two months the patient did not improve. He lost an additional six pounds and developed anorexia, increasing dyspnea, and pain in the midscapular region. He was hospitalized elsewhere for one week and was successfully treated for a right lower lobe pneumonia. He was readmitted to Strong Memorial Hospital in February 1968.

On examination he appeared cachectic and

From the Department of Medicine, Rochester General Hospital, Rochester, New York.

This study was supported in part by United States Public Health Service Grant HE-5500 and the Genesee Valley Heart Association.

Received for publication August 3, 1971.

Reprints: Dr. Robert V. Schnitzler, Department of Medicine, Rochester General Hospital, 1425 Elmwood Avenue, Rochester, New York 14620.

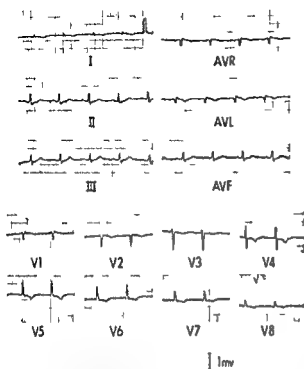


Fig. 1 Initial electrocardiogram taken in December 1967 showing normal sinus rhythm, some decrease in QRS voltage and generalized non-specific T wave abnormalities.

chronically ill. The blood pressure was 92/70 without paradox, pulse rate was 95 beats per minute and respirations were 30 per minute and shallow. The jugular venous pressure measured 9 cm above the sternal angle. A left cervical lymph node was palpable. Dullness decreased breath sounds and rales were present at both lung bases. The cardiac findings were similar to those described in the first admission except for further cardiomegaly. The liver was palpable 4 cm below the right costal margin and 2+ ankle edema was present.

The hematocrit was 38 per cent, white blood count was 19,100 with a normal differential and no abnormalities of the peripheral blood smear were seen. Urinalysis was negative. Prothrombin time was 45 per cent of normal. Blood urea nitrogen, serum electrolytes, total protein and protein electrophoresis were all normal. In addition, normal values for blood glucose, serum alkaline phosphatase, uric acid, calcium, phosphorus and glutamic oxalacetic transaminase were obtained.

Further cardiomegaly and bilateral pleural effusions were demonstrated on the roentgenogram of the chest. The ECG showed loss of anterior force in the horizontal plane in addition to low voltage and T wave inversion in Leads I, AV_L , and V_1 . CL_{12} cells were consistently observed on putum cytological examination.

Diuretic therapy was instituted without significant improvement and the patient continued to deteriorate. Pericardiocentesis was attempted on the seventh hospital day but no pericardial fluid was obtained. Lymphoid and histiocytic hyperplasia were reported on the biopsy specimen of a left axillary lymph node.

Table I Results of cardiac catheterization

Variables	Values
Cardiac index (L/min/M ²)	3.23
Heart rate (beat/min)	75
Stroke index (ml/beat/M ²)	43.4
Pressures (mm Hg)	
Right atrium	a = 10 v = 11 mean = 7
Left atrium	v = 35 mean = 18
Pulmonary artery	phasic = 58/70 mean = 37
Systolic artery	phasic = 103/63 mean = 80

On the twelfth hospital day, the patient's blood pressure fell to 88/60 and his pulse rate increased to 110 beats per minute. Pericardiocentesis was again performed with removal of 100 ml of bloody pericardial fluid. The specific gravity of the fluid was 1.014, its content was total protein 2.7 Gm per cent. There were 23.5 white cells of which 84 per cent were lymphocytes. Cultures for bacteria and fungi were negative. However, white blood count was persistently elevated. On the nineteenth hospital day, the patient's blood pressure fell further to 66/50, his pulse rate rose to 128 beats per minute and his respirations were 40. The jugular venous pressure rose markedly but fell during inspiration. The ECG and roentgenogram of the chest remained unchanged. On the twentieth hospital day, the patient died.

Discussion

DR JULES COHEN: This was a 51-year-old man who developed symptoms of rapidly progressive biventricular cardiac failure, who was poorly responsive to the usual modes of therapy. His physical examination had been normal a year and a half prior to the onset of his symptoms and he was dead within eight months after the disability began. Signs of atrioventricular valve incompetence were present on examination and at cardiac catheterization. At angiography a mediastinal mass lesion was demonstrated. This sequence of events, and the clinical findings were perfectly compatible with a primary mediastinal malignancy involving the heart.

We should try to examine the following questions raised by this case: (1) How might the mass lesion have been responsible for the clinical picture? In particular, what if any was the relationship between the mass lesion and the A-V valve incompetence?



Fig 2. A and B. Initial chest roentgenograms, December 1967. Posteroanterior (A) and lateral (B) views. The films show the massively enlarged cardiac silhouette with its irregular outline, the obscuration of the right hilum, posterior deviation of the esophagus, the left pleural effusion, and evidence of pulmonary venous hypertension.

tence? (2) Was the lesion a primary pericardial or a myocardial neoplasm?

Let us consider first the pathophysiology of the patient's symptoms. His cough, a common symptom in patients with mediastinal tumor, may have resulted from direct local irritation. On the other hand, it may have been the result of left atrial hypertension. The associated pulmonary venous hypertension may have led not only to interstitial pulmonary edema, but also to edema of the bronchial mucosa and to conditions conducive to the establishment of bronchitis. These disturbances, coupled with pleural effusion, very likely resulted in his exertional and nocturnal dyspnea and in his orthopnea.

This patient's elevated left atrial pressure was, I believe, largely due to mitral valve incompetence. A sizable V wave was present in the left atrial pressure tracing and the nadir of the rapidly descending reached 0 to 7 mm Hg (Fig 3). This suggests that there was little mitral obstruction and that left ventricular diastolic pressure probably was not substantially elevated. Therefore the patient probably did not have significant intrinsic left ventricular

dysfunction. Taken together with the substantial inequality in the atrial pressures, this fact makes it unlikely that pericardial restriction played the dominant role in the raised cardiac filling pressures at this point.

One element in the picture suggests another possible basis for raised pulmonary venous pressures, and that is localized pulmonary venous obstruction due to the mediastinal mass lesion itself. Could Dr Lipchik please review the films and, in particular, tell us whether there was preponderant pulmonary congestion or edema in one lung or the other? If this is the case, do the findings correlate angiographically with the site of pulmonary venous obstruction?

DR ILLIOT O. LIPCHIK. The first series of films (Fig 2) taken on December 7, 1967, with barium swallow and oblique views show a massively enlarged heart shadow with irregular outlines, particularly on the right and with the right hilum obscured (hilum overlay sign).¹ The barium-filled esophagus is displaced posteriorly by this large heart and by mediastinal shadow. There is a massive pleural effusion on the left side only, which depressed the dia-

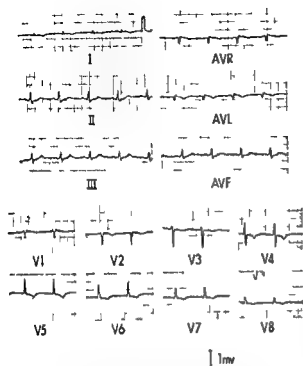


Fig. 1 Initial electrocardiogram taken in December 1967 showing normal sinus rhythm, some decrease in QRS voltage and generalized non-specific T wave abnormalities.

chronically ill. The blood pressure was 92/70 without paradox pulse rate was 95 beats per minute and respirations were 30 per minute and shallow. The jugular venous pressure measured 9 cm above the sternal angle. A left cervical lymph node was palpable. Dullness decreased breath sounds and rales were present at both lung bases. The cardiac findings were similar to those described in the first admission except for further cardiomegaly. The liver was palpable 4 cm below the right costal margin and 2+ ankle edema was present.

The hematocrit was 38 per cent, white blood count was 19,100 with a normal differential and no abnormalities of the peripheral blood smear were seen. Urinalysis was negative. Prothrombin time was 45 per cent of normal. Blood urea nitrogen, serum electrolytes, total protein and protein electrophoresis were all normal. In addition, normal values for blood glucose, serum alkaline phosphatase, uric acid, calcium, phosphorus and glutamic oxalacetic transaminase were obtained.

Further cardiomegaly and bilateral pleural effusions were demonstrated on the roentgenogram of the chest. The ECG showed loss of anterior force in the horizontal plane in addition to low voltage and T wave inversion in Leads I, aVL and V₁. Class I cells were consistently observed on sputum cytological examination.

Diuretic therapy was instituted without significant improvement and the patient continued to deteriorate. Pericardiocentesis was attempted on the seventh hospital day but no pericardial fluid was obtained. Lymphoid and histiocytic hyperplasia were reported on the biopsy specimen of a left axillary lymph node.

Table I Results of cardiac catheterization

Variables	Values
Cardiac index (L/min/M ²)	3.23
Heart rate (beats/min)	75
Stroke index (ml/beat/M ²)	43.4
Pressures (mm Hg)	
Right atrium	a = 110 v = 11 mean = 7
Left atrium	v = 35 mean = 18
Pulmonary artery	phasic = 58/20 mean = 32
Systemic artery	phasic = 105/65 mean = 80

On the twelfth hospital day the patient's blood pressure fell to 88/70 and his pulse rate increased to 110 beats per minute. Pericardiocentesis was again performed with removal of 100 ml of bloody pericardial fluid. The specific gravity of the fluid was 1.014, its content was total protein 2.7 Gm per cent. There were 2,375 white cells of which 81 per cent were lymphocytes. Cultures for bacteria and fungi were negative. However, white blood count was persistently elevated. On the nineteenth hospital day the patient's blood pressure fell further to 76/50, his pulse rate rose to 128 beats per minute and his respirations were 40. The jugular venous pressure rose markedly but fell during inspiration. The ECG and roentgenogram of the chest remained unchanged. On the twentieth hospital day the patient died.

Discussion

DR. JULES COHEN: This was a 51-year-old man who developed symptoms of rapidly progressive biventricular cardiac failure, who was poorly responsive to the usual modes of therapy. His physical examination had been normal a year and a half prior to the onset of his symptoms and he was dead within eight months after the disability began. Signs of atrioventricular valve incompetence were present on examination and at cardiac catheterization. At angiography a mediastinal mass lesion was demonstrated. This sequence of events and the clinical findings were perfectly compatible with a primary mediastinal malignancy involving the heart.

We should try to examine the following questions raised by this case: (1) How might the mass lesion have been responsible for the clinical picture? In particular, what, if any, was the relationship between the mass lesion and the A-V valve incompetence?



Fig. 3 A and B Pulmonary angiogram done in December 1967 Anteroposterior view (A) and lateral view (B)
See text for details

In summary, there is a large mediastinal mass intricately involved with the cardiac silhouette displacing and compromising the left atrium and ventricle as well as displacing the esophagus and left pulmonary arteries backward with moderate narrowing and encasement of the right pulmonary artery and with a massive and persistent left pleural effusion. There is a filling defect seen in the pulmonary vein draining the left upper lobe with the suggestion of occlusion of the veins from the left lower lobe.

DR. JULES COHEN: The anatomic evidence thus suggests that pulmonary venous occlusion or obstruction may have accounted in part for this patient's respiratory symptoms as it may in other patients with mediastinal tumor. On the other hand in this case the pulmonary artery diastolic pressure was equal to the left atrial pressure. Therefore the catheterization data also indicate that the patient had little pulmonary vascular obstruction especially considering the normal total pulmonary blood flow.

That being the case it appears unlikely that this obstruction resulted in increased resistance to total pulmonary blood flow even if the tumor was obstructing one or more pulmonary veins. Localized obstruction could account for the findings described by Dr. Lipchik. The elevated mean pressure in the main pulmonary artery in this case seems more likely reactive and the result of the elevated left atrial pressure due to mitral incompetence.

Clinical evidence of right heart failure was also present and this may have been the result of a combination of the pulmonary hypertension and perhaps of tricuspid incompetence—the latter suggested by the initial examination. Alternatively obstruction to caval blood flow (not an uncommon consequence of mediastinal and especially of pericardial tumor) might have been present and might have contributed to systemic fluid retention. However the transmission of a right atrial pressure wave to the jugular venous pulse suggests that at least superior vena cava obstruction was not present. Finally had the tumor infiltrated the right ventricular myocardium or largely impaired right ventricular filling by virtue of pericardial obliteration the resulting restrictive process might have contributed to right ventricular failure. But the form of the right ventricular pressure pulse was not that of pericardial or myocardial restriction.

The physiologic findings therefore suggest that the left heart failure here probably was largely related to the demonstrated mitral incompetence although localized pulmonary venous obstruction with localized pulmonary edema may also have contributed to the picture. The right heart failure may have been more complicated and the result of a combination of reactive pulmonary hypertension, tricuspid valve incompetence and possibly though less likely the addition of caval obstruction and/or involvement of the right ventricular

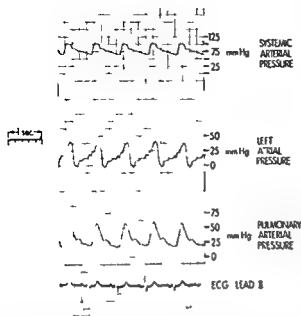


Fig 3 Results of cardiac catheterization December 1967. The systemic arterial pressure was normal but both the pulmonary arterial and left atrial mean pressures were raised and a prominent V wave was present in the left atrial pressure pulse. The pulmonary artery diastolic pressure and left atrial mean pressure were nearly equal suggesting that significant generalized pulmonary venous obstruction was not present.

phragm and impinges upon the superior aspect of the air filled gastric fundus. On the Bucky overpenetrated film of the chest, the pleural effusion can be seen collecting alongside the mediastinum and obliterating the paravertebral and aortic densities. There is no evidence of calcification, air fluid levels or significant atelectasis. The upper lobe veins are dilated indicating pulmonary venous hypertension.

The chest film two and a half months later (Fig 4) shows further enlargement of what appears to be a large cardiomedastinal density with complete obliteration of the left cardiac border and increased effusion on the left side. The bones do not show any evidence of metastatic disease. There are old healed rib fractures on the right. The trachea is midline.

Shortly after the first series of chest films, both a pulmonary angiogram and a left cineangiogram were performed with the injection of 40 ml of 75 per cent Hypaque solution into the main pulmonary artery followed by the injection of the same amount of contrast material directly into the left atrium. This latter study was performed with a Brocken-



Fig 4 Chest roentgenogram taken in February, 1968. See text for details.

brough catheter, passed transeptally from the right to the left atrium. Cine films were obtained at 60 frames per second.

The pulmonary angiogram (Fig 5) shows marked narrowing of the main right pulmonary artery as it traverses the mediastinum. The bifurcation of the right pulmonary artery appears normal with good visualization of the branches of the upper and lower lobes, showing no abnormality. There is prolonged holdup of contrast material into the arteries to the lingula and lower lobes. These vessels are displaced posteriorly and are somewhat narrowed. There is no evidence however of proximal pulmonary occlusions. The venous return from the right lung and the left upper lobe is normal.

The cine angiogram showed a normal to small left atrium with an extrinsic mass compromising the left atrium medially and from below. Reflux into the veins from the right lung showed no abnormality whereas there is a filling defect in the confluent vein from the left upper lobe. There was no reflux into the veins of the left lower lobe. The left ventricle is normal in size with rather poor contractions, particularly of the lateral aspect. The mediastinal density extends for several centimeters beyond the defined lumen of the ventricle out almost to the chest wall.



Fig 6 Interlacing bundles of spindle cells with hyperchromatic nuclei and scant cytoplasm form the solid portion of the tumor (Hematoxylin and eosin. Original magnification on X280)

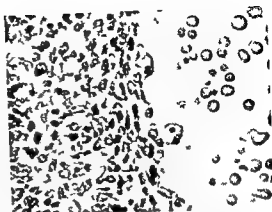


Fig 7 The cystic areas are lined by epithelial like cells. The cytoplasmic vacuolated inclusions seen in these cells contain mucopolysaccharide. Both these and the globules seen within the cyst were stained with periodic acid Schiff and the colloidal iron method (Hematoxylin and eosin. Original magnification X480)

heart muscle in the region of the atrioventricular valve rings thereby contributing to the A V valve incompetence. From the anatomic data, impingement of the tumor on the left atrium posteriorly inferiorly and superiorly and impingement on the pulmonary arteries is to be expected. Speaking strictly statistically, either primary mesothelioma or sarcoma of the pericardium would be most likely.¹⁴

Pathologic findings

DR ERICA SCHENK. When the thorax was opened a 20 by 17 by 16 cm mass which compressed both lungs and pushed them into the upper portion of the thoracic cavity was found in the mediastinum. The pleural surfaces were smooth except for a few fibrous adhesions between the visceral pleura and the generally smooth surface of the tumor mass. The right pleural cavity contained 1,500 ml and the left cavity contained 2,100 ml of thin red tinged slightly cloudy fluid. The excised mediastinal mass weighed 787 Gm and contained the heart, the ascending aorta and arch, the pulmonary artery and veins, the trachea and its bifurcation and the left and right main bronchi and esophagus.

The pericardial sac was obliterated and the tumor extended to the surface of the heart. Sections through the tumor showed variable structural features. Both cystic and solid areas were present. The cysts were single and multiloculated, some were filled with clear yellow fluid and others with grayish yellow friable or gelatinous mate-

rial. The solid areas ranged from soft and yellow to firm and gray. Although all of the contents in the anterior and posterior mediastinum were surrounded by this tumor, there appeared to be no grossly apparent extension into these structures.

The heart could not be dissected from the tumor mass which completely surrounded and encased it. Both left and right ventricles were moderately dilated with some flattening of the trabeculae carneae. In contrast, both atria appeared compressed and small. There was also compression of the pulmonary artery and veins.

Microscopic examination showed most of the tumor to be composed of spindle shaped cells arranged in a regular interlacing pattern. The spindle cells were generally small with oval or irregular hyperchromatic nuclei and a scant amount of cytoplasm (Fig 6). Prominent nucleoli and mitoses were infrequent. Special stains for reticulum and collagen showed these elements associated only with blood vessels within the tumor. The cystic areas were irregularly lined by epithelial like cells with abundant cytoplasm which contained periodic acid Schiff (PAS) staining material. The cystic spaces were filled with desquamated cells and globules which stained with both the periodic acid Schiff and colloidal iron methods for mucopolysaccharides (Fig 7). Spindle shaped tumor cells infiltrated the epicardium as well as the adventitia of the large arteries and veins in the superior

myocardium with tumor. There was no clinical or hemodynamic evidence of obstruction to outflow from either ventricle. However, patients with tumor encircling and obstructing either the pulmonary artery or the aorta or both have been described, and this possibility should be kept in mind in the evaluation of such patients. In any case it seems here that much of the clinical picture was secondary to the substantial A V valve incompetence that accompanied the basic pathology.

What are the possible mechanisms of A V valve incompetence in patients like this? Intracardiac tumor may mechanically interfere with valve leaflet movement. I don't think this is the case here because usually such patients demonstrate obstruction to flow as well, and there was no clinical or hemodynamic evidence of either mitral or tricuspid obstruction. Intraventricular tumor may involve the supporting structures of the valve and impair valve closure but angiographically the tumor in this case did not appear to involve the left ventricular cavity. Actual invasion of the myocardium may produce enough ventricular dysfunction to dilate the ventricle and the A V valve ring, thereby producing functional A V valve incompetence. As we discussed earlier, the catheterization and angiographic data do not support such an explanation for the mitral incompetence, but this remains a possible explanation of the tricuspid incompetence. Endocarditis might supervene in a patient with a mediastinal malignancy and produce A V valve lesions, but there is really nothing to suggest this complication in this patient. Conceivably pericardial tumor especially might produce coronary obstruction and lead either to left ventricular or papillary muscle dysfunction and mitral incompetence on this basis.² It also has been suggested that tumor invasion of the pericardium and the heart may sufficiently impair cardiac motion or distort the position of the heart and the A V valve rings so that valve closure is impaired. While such a hypothesis is by no means proved, this also seems a reasonable explanation of the A V valve incompetence in this case. Actual destructive invasion of the tumor into the valve substance itself is a possibility, in view of the impingement of the tumor on the atrial shadow inferiorly at angiography.

I want to consider the last point now, and present the arguments for this being a primary cardiac neoplasm rather than a primary tumor, of the lung for example, with spread to the heart. I also want to examine the basis for considering this a lesion of the pericardium rather than primarily of the myocardium or endocardium.

I think one would have expected other clinical evidence of a primary lung lesion or of a lymphoproliferative disorder or of some other more distant malignancy if the mediastinal mass lesion had been secondary to such a process. Furthermore, unless the malignancy had produced a sizable pericardial effusion with tamponade, which did not seem to be the case here, one would not have expected the cardiac disability to have so dominated the clinical picture, or to have been so rapidly progressive. In addition, the radiographic appearance of the cardiac silhouette is suggestive of a primary cardiac or pericardial lesion.

Finally, the clinical and, in particular, the radiographic findings suggest that we are dealing with a primary pericardial lesion rather than with a myocardial or endocardial lesion. Although it is somewhat surprising that the tumor did not produce more of a restrictive process, the mass seems external to the left atrium and ventricle angiographically. It has produced a hemorrhagic pericardial effusion. In contrast, there is no evidence of obstruction to blood flow within the heart, which one might expect of an endocardial mass lesion.³ Neither clear ventricular dysfunction nor conduction disturbances were present, and one might have expected these in a tumor which had significant myocardial spread.⁴ One would certainly have expected either obstruction to intracardiac flow or ventricular dysfunction from an endocardial or myocardial tumor which had produced this degree of cardiac enlargement and of compression external to the heart itself. I suppose it's possible that an angiosarcoma arising from one of the pulmonary veins could have produced the picture, but here again I would have expected to see an intracavitary lesion extending into the left atrium as well.

To conclude then, I think the evidence favors an extensive primary pericardial neoplasm. We may also hear from Dr Schenk that the tumor had invaded the

Fundamentals of clinical cardiology

The jugular pulse in pericardial constriction Its differentiation from that of cardiomyopathy

Charles P. Liss, MD*

Gary Hood, MD**

Morton E. Tatel, MD

Indianapolis, Ind

Differentiation of cardiomyopathies especially of the restrictive type from constrictive pericarditis is often a most difficult clinical problem. Symptoms reflecting restriction may dominate each heart size may be normal or slightly enlarged in both bedside examination of the external jugular pulse may reveal distended veins with a rapid Y descent. Cardiac catheterization frequently does not resolve the issue and often thoracotomy with pericardial or myocardial biopsy is required for a definitive diagnosis.

Analysis of the jugular pulse recording of the phonocardiogram has proved to be quite useful in clinical assessment of these difficult patients. In this study we have attempted to evaluate critically the diagnostic worth of phonocardiography with jugular pulse analysis in this difficult distinction and to compare its diagnostic value to that of cardiac catheterization.

Materials and methods

Phonocardiograms with external jugular pulse recordings from 12 patients with

proven constrictive pericarditis and 12 patients with cardiomyopathies were analyzed. All showed the square root configuration in the jugular pulse recording. Phonocardiograms were obtained from 15 normal subjects who served as controls.

Indirect jugular pulses were recorded by the method described by Tavel.¹ A funnel shaped pick-up device with an open end (2.5 cm diameter) was held over the internal jugular vein usually about 1 cm above the clavicle and 1 cm to the right of the sternoclavicular joint between the manubrial and clavicular insertions of the sternocleidomastoid muscle. The open end of the funnel was angled downward toward the diaphragm at approximately 45 degrees. Tracings were recorded during held expiration in the recumbent position with the head elevated on one pillow. The funnel was connected to a piezoelectric microphone (Sanborn No 374). The electrical signals were recorded graphically with an Electronics for Medicine Recorder (Model DR 8). The incoming signals were filtered with a band pass filter set at a range of 0.1

*With the technical assistance of James E. Swartz.

From the Department of Medicine, Indiana University School of Medicine and the Harrison Institute of Cardiology, Marion County General Hospital, Indianapolis, Ind.

Supported in part by the Herman C. Krannert Fund, Eli Lilly and Company, United States Public Health Service Grants HE-05815-06, HE-6308, HTS-5363 and HE-5749 and the Indiana Heart Association.

Requests for reprints to Morton E. Tatel, MD, Feller Hall, Room 110, Indiana University Medical Center 1100 W. Michigan St., Indianapolis, Ind 46202.

Trainee in Cardiology, Department of Medicine, Indiana University School of Medicine.

Senior Medical Student, Indiana University School of Medicine.

mediastinum, but there was no invasion of the myocardium or walls of the blood vessels. Similarly, no extension into the trachea or esophagus was apparent on any of the sections. There were no metastases to lymph nodes or other organs. Other significant pathologic findings were marked bilateral acute and chronic congestion of the lungs, bilateral atelectasis of the lower lobes of the lung, hepatomegaly (2,200 Gm) and splenomegaly (260 Gm) with chronic congestion, and ascites (1,000 ml).

The localization of this tumor in the pericardial region and its histologic appearance, an admixture of spindle cells and pseudoglandular or cystic elements, indicate that this is a fibroepithelial or mixed type of mesothelioma of the pericardium.⁷ It is further classified as a benign or nonaggressive mesothelioma because it remained confined to the pericardial region and even in this area its infiltrating proclivity was minimal.

The number of mesotheliomas of the pericardium which have been reported and reviewed is still small^{7,9} and there is controversy about certain aspects of these tumors. It is not clear whether some of the more malignant varieties with extra pericardial spread arose from pericardium or from some other site such as the pleura. The pure spindle cell varieties have not been uniformly accepted as mesothelial in origin and are referred to as fibrosarcomas in some reports.¹⁰ Mesotheliomas arising from the pleura and peritoneum often secrete mucoid material containing hyaluronic acid, which may be present in the effusions produced by these tumors.^{11,12} One previous attempt to demonstrate polysaccharide in tissue sections from a benign mixed mesothelioma of the pericardium was unsuccessful.¹³ The presence of cells and secretory material which stain with the periodic acid-Schiff and with the colloidal iron method in our case indicates that the pericardial mesotheliomas are capable of producing an acidic mucopolysaccharide, although its production like the histologic pattern may be more variable than that seen with pleural and peritoneal mesotheliomas.

The dysfunction resulting from the pres-

ence of this tumor must have been due to extrinsic compression of the heart and blood vessels at the base of the heart. The atria and pulmonary artery and veins were apparently most obviously compressed. There is no morphologic explanation for the proposed mitral valve incompetence. The circumference of the valve was of average size, and there was only a moderate degree of left ventricular dilatation. The encasing tumor mass may have 'fixed' the size and shape of the heart so as to produce valvular insufficiency.

FINAL ANATOMIC DIAGNOSIS Benign mixed (fibroepithelial) mesothelioma of the pericardium, blood-tinged pleural effusions (1,500 ml right, 2,700 ml left), atelectasis of both lower lobes of lungs, acute and chronic congestion of lungs, congestive hepato-splenomegaly, ascites.

REFERENCES

- 1 Felson B. The mediastinum. Semin Roentgenol 1:41 1969
- 2 Cardozo E L and Saltet J F. A case of mesothelioma pericardii. Acta Med Scand 178:301 1965
- 3 Goodwin J F. The spectrum of cardiac tumors. Am J Cardiol 21:307 1968
- 4 Harvey W P. Clinical aspects of cardiac tumors. Am J Cardiol 21:378 1968
- 5 Mahaim I. Les tumeurs et les polypes du coeur. Paris 1945. Masson et Cie.
- 6 Yraola L et al. Primary pericardial mesothelioma. Acta Cardiol 15:781 1960
- 7 Daw C J, Wood D A and Mitchell S. Diffuse fibrous mesothelioma of the pericardium. Cancer 6:794 1953
- 8 Pietra G C, Silber F, Levin H and Pick A. Clinical pathologic conference. Am Heart J 73:545 1968
- 9 Sytnan A L and MacAlpin R N. Primary pericardial mesothelioma: report of two cases and review of the literature. Am Heart J 81:760 1971
- 10 Pader F and Karschner P A. Primary sarcoma of the pericardium. Am J Cardiol 14:399 1964
- 11 Meyer K and Chaffee E. Hyaluronic acid in the pleural fluid associated with a malignant tumor involving the pleura and peritoneum. J Biol Chem 133:83 1940
- 12 Dvoskin S. Mesothelioma of the peritoneum. A case report in which ascitic fluid contained hyaluronic acid. Ann Intern Med 40:809 1954
- 13 Thomas J and Phythyon J M. Primary mesothelioma of the pericardium. Circulation 15:385 1957

Table III Summary of mean values

Patient group	A_2V	P_4	PA_4	$\overline{P_4}$	R_1	R_{1A}	$\overline{R_1}$	$R_1 \overline{R_1}$
Normal \pm S.D.	0.10 ± 0.07	—	—	—	—	—	—	—
Cardiomyopathy \pm S.D.	0.07 ± 0.043	57 ± 16.1	79 ± 9.9	38 ± 9.6	55 ± 13.8	13 ± 5.1	14 ± 6.1	43 ± 11.1
Constrictive pericarditis \pm S.D.	0.00 ± 0.06	34 ± 8.4	18 ± 6.9	77 ± 7.3	33 ± 9.3	15 ± 6.5	15 ± 7.5	20 ± 5.7
P-value	<0.01	<0.05	N.S.	N.S.	<0.01	N.S.	N.S.	<0.01

Abbrev: mean S.D. = la dard de lat na de S. = not significant. Other abbreviations as in Table I.

proven diagnosis diagnosis was made on the basis of the entire clinical picture including electrocardiogram chest x ray fluoroscopy catheterization data and clinical course. None of the patients manifested evidence of significant tricuspid insufficiency.

Results

Data from phonocardiograms and cardiac catheterization are presented in Tables I and II. The mean pressures for the pulmonary artery, right ventricle and right atrium and the difference between right ventricular systolic and right atrial mean pressures are listed in Table III. They show elevation of all pressures in both groups; however, the right ventricular systolic pressure is elevated to a greater degree in the cardiomyopathy group than in the constrictive group ($p < 0.01$). Further, there is a striking difference ($p < 0.001$) between the differences of right ventricular systolic and right atrial mean pressures in the two groups. The mean A_2V interval (Table III) for the cardiomyopathy group is 0.07 second and for the constrictive pericarditis group 0.00 second; this difference is also significant ($p < 0.01$). Fig. 1 illustrates the distribution of the A_2V intervals in the normals and both patient groups. It can be seen that in all normal controls the A_2V interval exceeded 0.03 second. The cardiomyopathy group was similar with only 3 of 12 patients having an A_2V interval less than 0.03 second, with the remainder exceeding this value. Conversely, 9 of 17 in the constrictive pericarditis group showed an A_2V less than 0.03 second, while in only 3 patients the A_2V interval exceeded 0.03 second. Figs. 2 and 3 show typical examples of each group.

Discussion

There has been an abundance of literature pointing out the similarities and differences in clinical and hemodynamic manifestations of constrictive pericarditis and cardiomyopathies.²⁻⁶ While the contour of the right atrial pressure pulse seen in constrictive pericarditis was once felt to be pathognomonic for this entity,⁷ it is now well established that disease entities which restrict ventricular filling by involving the endocardium or myocardium^{1,6} may produce an identical pattern.

Phonocardiography may provide a useful and easily performed adjunct in this difficult clinical problem. While the basic contour of the jugular pulse wave in cardiomyopathy and constrictive pericarditis may be identical, the earlier appearance of the V wave in constriction usually distinguishes the two groups. As can be seen in Fig. 1, an A_2V interval of less than 0.03 second is strong evidence for constrictive pericarditis; an A_2V exceeding 0.03 favors cardiomyopathy.

While the precise mechanisms underlying these differences in timing are subject to speculation, we feel that correlation with catheterization data (summarized in Table III) provides an explanation. In the cardiomyopathy group there is striking elevation of right ventricular systolic pressure with only a slight increase in diastolic pressure and in right atrial pressure. As a result, the right ventricular pressure must fall a considerable distance before it drops below right atrial pressure and allows the tricuspid valve to open. The isovolumic relaxation period of the right ventricle is therefore relatively long and this is reflected in the long interval from the second sound to the V wave peak. On the other

Table I A_2V intervals and cardiac catheterization data of cardiomyopathy patients

Patient	A_2V	$P1_s$	$P1_d$	$\overline{P1}$	RI	RV_d	\overline{RI}	$RV - \overline{RI}$
E L	0 04	88	45	50	—	—	23	—
G L	0 00	30	14	19	30	9	8	22
C H	0 09	55	36	41	55	19	16	39
J L	0 11	—	—	—	—	—	—	—
S M	0 14	52	21	33	65	16	15	50
E S	0 01	—	—	—	—	—	—	—
I U	0 10	70	32	43	70	17	17	58
T W	0 14	56	28	39	56	15	15	41
K W	0 14	57	23	39	57	9	8	49
S S	0 09	53	32	39	53	4	5	48
A P	-0 08	75	43	53	75	20	24	51
G R	0 09	38	17	25	36	10	9	27
Mean	0 07	59	29	38	55	13	14	43

Abbreviations A_2V = interval from aortic closure to V wave peak (sec) $P1_s$ = pulmonary artery systolic pressure $P1_d$ = pulmonary artery diastolic pressure $\overline{P1}$ = mean pulmonary artery pressure RV = right ventricular systolic pressure RV_d = right ventricular diastolic pressure \overline{RV} = right atrial mean pressure $RV - \overline{RV}$ = difference between right ventricular systolic and right atrial mean pressures (all pressures in mm Hg)

Table II A_2V intervals and cardiac catheterization data of constrictive pericarditis patients

Patient	A_2V	$P1_s$	$P1_d$	$\overline{P1}$	RV	RV_d	\overline{RI}	$RV - \overline{RI}$
W W	-0 09	—	—	—	—	—	—	—
J S	0 06	27	10	16	27	6	8	19
D I	-0 02	31	18	24	32	15	14	18
D B	0 00	37	19	28	37	18	16	21
J S	-0 02	21	10	17	21	9	10	11
C S	0 11	36	18	25	36	10	13	23
B J	-0 03	—	—	—	—	—	—	—
M M	-0 04	42	22	32	42	20	16	29
H W	0 02	—	—	—	—	—	—	—
P W	0 04	45	30	36	47	31	31	16
A W	-0 09	—	—	—	—	—	—	—
L C	0 02	—	—	—	—	—	—	—
Mean	0 00	34	18	27	35	15	15	20

Abbreviations as in Table I

to 20 cycles per second (cps) Recording speed was 100 mm per second and time lines were set at 0.1 second intervals

The jugular pulse recording was analyzed and the interval from aortic closure to the peak of the V wave (A_2V) was determined A_2 rather than P_2 was used as a reference point because it is more easily identified in the phonocardiogram Five complexes were analyzed and average values were used

Right and retrograde left heart catheterization was performed on 10 of 12 patients with cardiomyopathies and 7 of 12

patients with constrictive pericarditis Pressures were recorded in all heart chambers, the pulmonary artery and a systemic artery dye curves were done to exclude a shunt Definitive diagnosis was made in two cardiomyopathy patients at autopsy (subendocardial fibroelastosis and amyloid) and an additional patient had a histologically normal pericardium at surgery Five patients with constrictive pericarditis had a definitive histologic diagnosis made by biopsy or necropsy study In the remaining patients i.e. those without a histologically

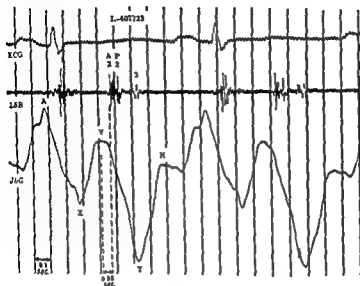


FIG 3 Example of findings typical for constrictive pericarditis $A_2V = -0.06$ sec

to our total group of patients the diagnosis would have been correct in 18 out of 24 patients. Tricuspid insufficiency with a pronounced and early V wave might potentially simulate pericardial constriction. The presence of the typical jugular contour and associated clinical findings of tricuspid disease however should allow one to distinguish it from pericardial constriction.

Phonocardiography with jugular pulse analysis provides a simple inexpensive noninvasive and reasonably accurate adjunct in the differentiation between cardiomyopathy and constrictive pericarditis. When correlated with the clinical presentation and other laboratory data it is quite helpful in this difficult clinical problem. When one further analyzes other components of the routine phonocardiogram especially the characteristic pattern of retraction seen in the apexcardiogram in constrictive pericarditis and the morphology of the X descent in the jugular pulse recording⁶ phonocardiography may even prove decisive in this difficult clinical problem.

Summary

Study of the indirect jugular pulse has potential value in differentiation of cardiomyopathies from constrictive pericarditis often a difficult clinical problem. Twelve patients with constrictive pericarditis were compared with 12 patients with cardio-

myopathy and 15 normal subjects. The interval between the aortic second sound and the jugular V wave peak (A_2V) was determined for each case. Nine of 12 patients with cardiomyopathy and all 15 normal subjects had an A_2V greater than 0.03 second while in 9 of 12 cases with constrictive pericarditis A_2V was less than 0.03 second. Thus using A_2V alone the distinction between cardiomyopathy and constrictive pericarditis could be made in 18 of our 24 patients. A_2V reflects the isovolumic relaxation time of the right ventricle. This is shortened in constrictive pericarditis because of a high right atrial pressure and relatively normal right ventricular pressure. Study of the jugular pulse in this manner provides a safe inexpensive and noninvasive adjunct in diagnosing constrictive pericarditis.

REFERENCES

1. Tavel M H. Clinical phonocardiography and external pulse recording. Chicago 1957 Year Book Medical Publishers Inc p 35.
2. Hetzel P H. Pressure pulses in the right side of the heart in a case of amyloid heart disease and in a case of idiopathic heart failure simulating constrictive pericarditis. Mayo Clin. Proc 28:107 1953.
3. Balchum O J, McCord M D and Blount S G Jr. The clinical and hemodynamic pattern in nonspecific myocarditis: a comparison with other entities also impairing myocardial efficiency. AM HEART J 52:130 1956.

A₂V INTERVALS FOR NORMALS, CARDIOMYOPATHIES AND CONSTRICTIVE PERICARDITIS

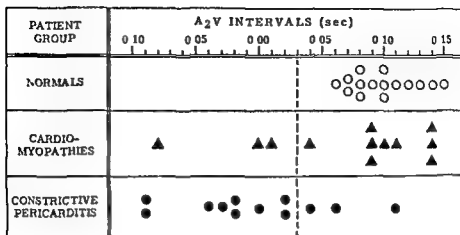


Fig. 1 Distribution of the Δ_2V intervals within the various groups

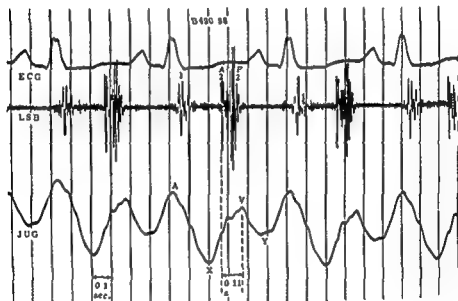


Fig 2 Example of findings typical for cardiomyopathy. $A_2V = 0.11$ sec

hand in constrictive pericarditis relatively normal right ventricular systolic pressure persists with an elevated diastolic pressure and right atrial pressure. Hence, isovolumetric relaxation of the right ventricle is short, producing a short or even negative A_2V interval.

Consideration of some individual patients in our study lends support to this hypothesis. Patients J S and C S (constrictive group, Table II) each had a right ventricular systolic to diastolic pressure ratio of greater than 3 to 1, which is unusual in constrictive pericarditis, in addition each had a relatively low mean right atrial pressure. The A_2V intervals for these pa-

tients were respectively 0.06 and 0.11 second more in keeping with cardiomyopathy. All other catheterized patients in the constrictive pericarditis group had right ventricular systolic to-diastolic pressure ratios less than 3:1. Patient A.P. (cardiomyopathy group, Table I) had an A_2V interval measuring -0.08 second. Note that his right atrial pressure was the highest recorded in this group.

Using the criteria outlined above, namely, that an A₂V interval less than 0.03 second favors constrictive pericarditis while a value exceeding this is consistent with cardiomyopathy, a high degree of diagnostic accuracy is attained. Applying these criteria

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

The medical treatment of angina pectoris IV Nitroglycerin as an antianginal drug

Wilbert S Aronow MD*
Long Beach and Irvine Calif

Nitroglycerin is considered by most physicians to be effective in the treatment of angina pectoris. However Master Jaffe and Dack¹ stated in 1939 that in 89 patients with angina pectoris due to coronary artery disease sublingual nitroglycerin was not better than a placebo in the treatment of angina pectoris.† Fisch and DeGraff² demonstrated in a double blind study that nitroglycerin administered sublingually to 9 patients with angina pectoris due to coronary artery disease at the onset of exercise induced angina was not significantly better than placebo in shortening the duration of the anginal attack. Sandler, Hahn, and Lawson³ also showed in a double blind study that nitroglycerin administered sublingually to 15 patients with angina pectoris due to coronary artery disease in doses of either 0.25 mg, 0.50 mg, or 1.0 mg at the onset of an episode of exercise induced angina did not cause any significant change in the duration of the anginal attack or in the duration of ischemic ST segment depression in the electrocardiogram (ECG) in comparison with placebo. Riseman and Brown⁴ reported that the

duration of exercise induced angina pectoris without medication was less than 1 minute in 18 of their 37 patients (49 per cent) with angina pectoris due to coronary artery disease. In 61 per cent of these 18 patients sublingual nitroglycerin did not alter the duration of anginal pain. In 22 per cent of these 18 patients sublingual nitroglycerin decreased the anginal attack by about one third. In 17 per cent of these 18 patients sublingual nitroglycerin increased the anginal episode by about one third. These investigators⁴ showed that the duration of exercise induced angina pectoris without medication lasted from 1 to 2 minutes in 16 of their 37 patients (43 per cent). In 62 per cent of these 16 patients sublingual nitroglycerin shortened the anginal episode. In 38 per cent of these 16 patients sublingual nitroglycerin did not alter the duration of the anginal pain. Riseman and Brown⁴ demonstrated that the duration of exercise induced angina without medication lasted from 2 to 3.5 minutes in 3 of their 37 patients (8 per cent). Sublingual nitroglycerin significantly shortened the duration of the anginal episode in all 3 of

*From the Cardiology Section, Medical Service, Long Beach Veterans Administration Hospital, and the University of California College of Medicine, Irvine, Calif.
Received for publication April 7, 1972.
Reprint requests: Wilbert S. Aronow, MD, Cardiology Section, Veterans Administration Hospital, Long Beach, Calif. 90801.

*Staff Cardiologist and Chief of Phonocardiography, Long Beach Veterans Administration Hospital, Associate Adjunct Professor of Medicine, University of California College of Medicine, Irvine, Calif.
†Personal communication from Dr. Master who feels that sublingual nitroglycerin is not effective in the treatment of angina pectoris.

- 4 Wood P Chronic constrictive pericarditis
Am J Cardiol 7:48 1961
- 5 Dye C L Rosenbaum D Lowe J C Behnke
R H and Genovese I D Primary myocardial
disease part I Clinical features *Ann Intern
Med* 58:426 1963
- 6 Robin E D and Burwell C S Hemodynamic
aspects of diffuse myocardial fibrosis *Circula-
tion* 16:730 1957
- 7 Hansen A T Eskildsen P and Gotzsche H
Pressure curves from the right auricle and the
right ventricle in chronic constrictive pericarditis
Circulation 3:881 1951
- 8 El Sherif A and El Said G Jugular hepatic
and precordial pulsations in constrictive peri-
carditis *Br Heart J* 33:305 1971

minutes prior to treadmill exercise caused an average increase of 125 per cent over the control value in the amount of exercise performed before the appearance of angina and an average increase of 121 per cent over the control value in the amount of exercise performed before the onset of ischemic ST segment depression. Fourteen of their 16 patients (88 per cent) exhibited more than a 50 per cent increase in exercise tolerance over the control value before the onset of angina pectoris. Goldstein and his associates⁴ demonstrated that nitroglycerin administered sublingually to 8 patients with angina pectoris due to coronary artery disease 3 minutes before upright bicycle ergometer exercise caused a significant increase in exercise capacity and a significant delay in the onset of ischemic ECG changes in comparison with placebo.

Detry and Bruce⁵ reported that 0.4 mg of nitroglycerin administered sublingually to 37 patients with angina pectoris due to coronary artery disease at the onset of treadmill exercise caused a significant increase in the maximal heart rate, a significant increase in the product of systolic blood pressure and heart rate and significantly less ischemic ST segment depression during and after exercise. Twelve of these 37 patients (38 per cent) were also symptomatically limited by dyspnea and fatigue rather than by chest pain. Parker, West and DiGiorgi¹² found that 0.5 mg of chewable nitroglycerin administered to 7 patients with angina pectoris due to coronary artery disease approximately 10 minutes prior to supine leg exercise caused only 2 of these 7 patients to experience angina and their angina was less severe than that experienced during the control period. The hemodynamic response to this exercise following prophylactic nitroglycerin was also normal in these 7 patients.

However, it should also be pointed out that in a double blind study Fisch and DeGraff² showed that nitroglycerin administered sublingually to 9 patients with angina pectoris due to coronary artery disease 10 minutes before upright bicycle ergometer exercise did not improve the exercise tolerance in comparison with placebo.

Needleman¹¹ reported that high doses of nitroglycerin administered 3 times a day

to rats produced tolerance to the blood pressure response of nitroglycerin. However, Modell¹³ pointed out that the development of tolerance to nitroglycerin from even unusually frequent clinical use was not common. We¹² reported in a double blind study that administration of sublingual isosorbide dinitrate for 4 weeks to 17 patients with angina pectoris due to coronary artery disease did not cause any clinical impairment of the effective response of angina pectoris to sublingually administered nitroglycerin.

Lange, Reid and Bernhard¹⁴ reported that non atheromatous coronary heart disease may develop on withdrawal from marked chronic nitroglycerin exposure. These investigators found that 8 of 160 female munitions workers (5 per cent) developed angina pectoris after withdrawal from nitroglycerin exposure for 48 hours. Two of these 160 munitions workers (1 per cent) developed prolonged episodes of coronary insufficiency and 3 of these 160 munitions workers (2 per cent) developed myocardial infarction with 1 of these 3 patients dying. This death occurred in a previously normal 40 year-old person. All but one of these survivors left the chronic exposure to nitroglycerin and improved. Their data suggest that some patients with or without coronary artery disease may develop withdrawal symptoms if nitroglycerin or other nitrite preparations are suddenly stopped after regular frequent heavy long term usage.

Finally, we agree with Modell¹³ that oral as opposed to sublingual administration of nitroglycerin is of little clinical value and that none of the nitroglycerin preparations designed for delayed absorption in the gastrointestinal tract have any merit. There are also no well controlled studies which show that nitroglycerin administered either orally in an ordinary tablet or in sustained release form or as a skin ointment is effective as an antianginal drug.

REFERENCES

1. Master A M, Jaffe H L and Dack S. The drug treatment of angina pectoris due to coronary artery disease. *Am J Med Sci* 197: 774, 1939.
2. Fisch S and DeGraff A C. Coronary vasodilators. *Dis Chest* 44: 533, 1963.
3. Sandler G, Ilahi M A and Lawson C W.

these patients. These investigators⁴ also found that 0.3 mg of nitroglycerin administered sublingually was as effective as 0.6 mg dose in relieving angina and was less likely to cause headache. A dose of 0.12 mg of sublingual nitroglycerin was, however, less effective than a 0.3 mg dose in relieving angina.

Using a standardized interview, Horwitz, Herman, and Gorlin⁵ questioned patients who had taken sublingual nitroglycerin for chest pain due to and not due to significant coronary artery disease as documented by coronary angiography. Almost all of their patients had used 0.3 mg or 0.4 mg nitroglycerin tablets and virtually all had used more than one tablet at a time. Horwitz, Herman, and Gorlin⁵ found that 37 of their 49 patients (76 per cent) with angina pectoris due to significant coronary artery disease reported that their anginal pain was usually or always relieved in less than 3 minutes after administration of sublingual nitroglycerin. Eighteen of these 49 patients (37 per cent) experienced consistent relief of their angina pectoris in less than 1 minute after administration of sublingual nitroglycerin. Eight of these 49 patients (16 per cent) regularly experienced relief of their anginal pain from 4 to 15 minutes usually about 5 minutes after administration of sublingual nitroglycerin. Relief of anginal pain in these patients was often incomplete. Four of these 49 patients (8 per cent) reported that nitroglycerin did not affect their chest pain. The patients with angina pectoris due to significant coronary artery disease who had delayed relief or no relief of their anginal pain following sublingual nitroglycerin tended to have more frequent and intense anginal pain, more coronary artery involvement by obstructive lesions, and more hemodynamic or wall motion abnormalities than those patients who experienced relief of their anginal pain within 3 minutes after administration of sublingual nitroglycerin.

Horwitz, Herman and Gorlin⁵ also reported that 4 of their 21 patients (19 per cent) with chest pain not due to significant coronary artery disease as documented by coronary angiography experienced relief of their chest pain within 3 minutes after administration of sublingual nitroglycerin. Nine of these 21 patients (43 per cent) ex-

perienced relief of their chest pain after more than 3 minutes usually after 5 minutes or more following administration of sublingual nitroglycerin. Eight of these 21 patients (38 per cent) reported that sublingual nitroglycerin was never effective in relieving their chest pain.

Our experience is that sublingual nitroglycerin is not necessary for treating a mild episode of angina pectoris. Cessation of exertion with motionless standing causes pooling of blood in the lower extremities and relieves angina. Sublingual nitroglycerin is, however, effective in treating a more severe episode of angina pectoris. We recommend using an initial dose of 0.3 mg which often suffices and is less likely to induce headache or other unpleasant side effects. Patients should be instructed not to take more than 2 to 3 sublingual nitroglycerin tablets over a period of 15 minutes for a prolonged anginal attack. Additional nitroglycerin should not be taken as the patient may be having an acute myocardial infarction.⁶ There is also the danger that the systemic hypotension and decreased coronary blood flow induced by sublingual nitroglycerin might also convert an episode of prolonged angina pectoris into a myocardial infarction.

Nitroglycerin, in our experience, is most useful as an antianginal drug when administered sublingually 2 to 3 minutes prior to performing activities or encountering stressful situations in which an anginal attack may be anticipated. Sandler, Ilahi, and Lawson⁷ reported in a double blind study that nitroglycerin administered sublingually to 12 patients with angina pectoris due to coronary artery disease in doses of 0.25 mg, 0.50 mg, and 1.0 mg 3 minutes prior to exercise significantly increased the amount of exercise performed before angina pectoris developed in comparison with placebo. There was no significant difference in the amount of exercise performed between these 3 doses of nitroglycerin. The 0.25 mg and 0.50 mg doses but not the 1.0 mg dose also significantly decreased the duration of the anginal attack.

MacAlpin, Alvaro, and Kattus⁷ showed that nitroglycerin administered sublingually to 16 patients with angina pectoris due to coronary artery disease in doses ranging from 0.3 mg to 0.6 mg 2 to 4

On the chemical nature of basophilic (mucoid) degeneration of myocardium

The term basophilic degeneration (BD) of myocardium is applied to the presence of a basophilic, finely granular material in the cytoplasm of isolated myocardial fibers. This condition is also known as mucoid or mucinous degeneration and cardiac mucoid. It was first recognized by Geipel¹ in 1903 and has been the subject of numerous studies. It is primarily a human condition although it has been seen exceptionally in animals. Its etiology is uncertain. The degree of BD found in a heart is mainly related to the age of the individual. There are three disease processes in which BD is usually present to a much greater degree than one would expect from age alone.²⁻⁴ These are (1) Lafora's disease (a familial form of myoclonic epilepsy) (2) hypothyroidism and (3) idiopathic myocardiopathy.

Very little is known of the significance mechanism of formation and chemical composition of BD. In a recent study by the writer⁵ BD was found in 88 per cent of the 135 hearts examined. Whereas it was never seen in patients who had died in the first decade of life, it was found in all individuals after the age of 11 years with only one exception. A definite correlation was found between increasing age and the extent of the degeneration.

BD's reaction was positive to these techniques all known to stain glycogen: periodic acid-Schiff, Lavan's iodine, Best's carmalum and Gomori's aluminum-iodine. It also stained with Mowry's colloidal iron and with Alcian blue (the latter when performed at a pH of 2.5). Stains for amyloid, DNA, RNA, elastic tissue, calcium and iron were negative. Incubation of the tissue sections with malt diastase for 30 min. (the usual time employed for the removal of glycogen) did not produce any appreciable effect. However, prolonged periods of incubation (up to 48 hours) with the same enzyme abolished the periodic acid-Schiff (PAS) positivity. If the sections or tissue blocks were pretreated with chloral hydrate or boiled in distilled water 30 min. of diastase was sufficient to completely remove the deposits of BD. Amyloglucosidase (α -1,4-glucan glucosylhydrolase) and pectinase were the only other enzymes tested which removed the deposits. By electron microscopy BD deposits were seen as sharply circumscribed foci composed mainly of short straight fibrils 60 to 70 Å in width running in a haphazard fashion with no axial periodicity. Scattered among the fibrils were a

few round dense granules 150 Å in diameter compatible with glycogen particles.

BD was isolated from myocardium containing extensive deposits using Pfleger's method⁶ hearts without BD were used as controls. The isolated material had a concentration of 0.92 µmoles of polyglucose per gram. It was completely degraded by the combined action of phosphorylase and debranching enzyme. Its infrared spectrum was practically identical to that of a sample of rabbit liver glycogen.

The results we have obtained with this combined histochemical ultrastructural and biochemical approach favor the interpretation that BD is basically composed of a glucose polymer (glucan or polyglucosan). It has many features in common with three other substances that can be found in human tissues: (1) corpora amylacea of the central nervous system (2) intraneuronal Lafora's bodies (seen in Lafora's disease) and (3) the deposits of abnormal glycogen present in glycogenosis IV.⁶ In all of these substances chemical studies have also indicated the polyglucosan nature of the deposits.

With the support of these observations we postulate that the branched glucan deposited in BD represents a relatively insoluble byproduct of glycogen metabolism possibly brought upon by an acquired relative deficiency of an enzyme (or enzymes) of the glycogenesis-glycogenolysis pathway.

Juan Rosas M.D.

Department of Pathology

Washington University School of Medicine

St. Louis, Mo. 63110

Eduardo F. Lescano M.D.

Hospital Regional

Mar del Plata, Argentina

REFERENCES

1. Geipel P. Untersuchungen über rheumatische Myokarditis. *Deutsch Arch. Klin. Med.* 83:175, 1905.
2. Harrman D G F, Millar J H D and Stevenson A C. Progressive familial myoclonic epilepsy in three families. Its clinical features and pathological basis. *Braun* 78:325, 1955.
3. Brewer D H. Myxoedema. An autopsy report with histochemical observations on the nature

Glyceryl trinitrate in angina pectoris *Lancet* 1:1130 1963

- 4 Riseman J L F and Brown M G The duration of attacks of angina pectoris on exertion and the effect of nitroglycerin and amyl nitrite *N Engl J Med* 217:470 1937
- 5 Horwitz L D Herman M V and Gorlin R Clinical response to nitroglycerin as a diagnostic test for coronary artery disease *Am J Cardiol* 29:149 1972
- 6 Prodder S H and Ayman D Harmful effects of nitroglycerin With special reference to coronary thrombosis *Am J Med Sci* 181:480 1932
- 7 MacAlpin R N Alvaro A B and Kattus A A Effect of propranolol and nitroglycerin on exercise tolerance in angina pectoris in Kattus A A Ross G and Hall V editors *UCLA forum in medical sciences No 13 Cardiovascular beta adrenergic responses* Berkeley Los Angeles and London 1970 University of California Press p 191
- 8 Goldstein R E Rosing D R Hedwood D R Beiser G D and Epstein S L Clinical and circulatory effects of isosorbide dinitrate Comparison with nitroglycerin *Circulation* 43:629 1971
- 9 Detry J M and Bruce R A Effects of nitroglycerin on maximal oxygen intake and exercise electrocardiogram in coronary heart disease *Circulation* 43:155 1971
- 10 Parker J O West III O, and DiGiorgi E The effect of nitroglycerin on coronary blood flow and the hemodynamic response to exercise in coronary artery disease *Am J Cardiol* 27:59 1971
- 11 Needleman P Tolerance to the vascular effects of glyceryl trinitrate *J Pharmacol Exp Ther* 171:98 1970
- 12 Modell W Clinical pharmacology of antianginal drugs *Clin Pharmacol Ther* 3:97, 1961
- 13 Aronow W S and Chesluk H M Evaluation of nitroglycerin in angina in patients on isosorbide dinitrate *Circulation* 43:61 1970
- 14 Lange R L Reid M S and Bernhard V M Non atheromatous coronary heart disease on withdrawal from chronic nitroglycerin exposure *Circulation* 44 (Suppl II) 44 1971

Recently Burch³ provided evidence that people live no longer any more — and emphasized that far more research should be undertaken into the factors which regulate aging. His Annotation makes somber reading. He showed that in the U.S.A. expectation of life at birth increased enormously in the present century until about 1950 when it reached a plateau. He thought that the expectation may actually be declining.

Although in comparison with the past, a far larger proportion of people nowadays live to a good age, it is not generally appreciated that expectation of life at late middle age has remained almost stationary as far back as records are available. Perhaps the earliest of life tables was constructed in 1687 by Halley⁴ of Halley's comet fame. He reported that in Breslau, Germany, expectation of life at 60 and at 80 years averaged about 12 and 5 years respectively. Three centuries later some corresponding data are as follows: Australians in 1907 17 and 6 years; South African whites in 1960 17 and 6 years; American Jews in 1965 15 and 5 years.⁵ From this and other information it would seem that while expectation of life at birth in the U.S.A. reached its apparent maximum 20 years ago, expectation at late middle age in Caucasian populations over a very long period has slightly improved at age 60 years and virtually not at all at age 80 years. For the few hundred population of U.S.A. since 1910 there has been an un doubted decline.

From the graph given by Burch³ in the U.S.A. expectation of life at birth has remained steady since 1930 not only for whites but also for non whites, the mean figure for the former is about 71 years and for the latter about 64 years — a difference of 7 years. This is very urban. Most if not all would have predicted with assurance that the difference would become progressively narrower with rise in the socio-economic conditions of non white. But this has not been the case. Burch³ considered the possibility that non Caucasian races may be genetically programmed to have a shorter life span than whites. He regarded this as unlikely. Yet the possibility cannot be excluded. The most striking suggestion that comes to mind in this regard concerns Indians in India compared with Indians whose forebears emigrated to South Africa. In 1951 at Ramana gram in Mysore, South India, a general health study was made on a population of 73 000 rural Indians. It was found inter alia that of the leading cause of death the first ten were infections. Of persons aged 50 years or more 14.5 per cent reached 70 years of age. In South Africa the age structure of three distinct groups of urban Indians (330 families) living near Johannesburg has been studied. Almost all were in fairly comfortable circumstances. Leading causes of death among them were coronary heart disease, pneumonia, strokes, cancer and diabetes. Of persons aged 50 or more years, only 9 per cent had reached 80 or more years. Although the number of families studied is relatively small, the results obtained are in agreement with the Census figures for 1960, namely 11 per cent for the half million Indian community in South Africa.⁶ But this figure has decreased since 1951 when it was 15 per cent.⁶ In this respect populations normally show an increase, not a decrease with time. Thus despite out-

wardly vastly improved environmental conditions South African urban Indians at late middle age have a somewhat lower expectation of life compared with their outwardly far less fortunate compatriots in rural India. In consonance with this information it is interesting to note that among urban dwellers both in India and in South Africa, severe atheroma and peak frequency of myocardial infarction apparently occur a decade earlier in Indians than in whites.^{7,8} Moreover in India there is evidence that urban dwellers in poor circumstances have a greater frequency of coronary heart disease than would be expected.⁹ Nor is the situation described peculiar to South African Indians. In an investigation of 140 Malay families in a township in Johannesburg it was found that 85 per cent owned cars and 90 per cent had Bantu servants. Yet of persons 50 years or older, only 9 per cent were 10 or more years of age. In comparison with the foregoing, the corresponding proportion for South African whites in the 1960 Census was 22 per cent.¹⁰ In England and Wales in 1961 the proportion was 24 per cent.¹¹ A further fact of importance is that among South African Bantu at a socio-economic level far below that of local Indians and Malays, the corresponding figures are relatively high, namely 17 to 18 per cent.¹² It therefore appears that Indians have a malignant hyper-reactivity possibly of genetic origin to certain noxious factors which are linked with urban life.¹³

Briefly it would seem that

1 In contexts of modern life, ethnic groups may differ markedly in their apparent maximum expectation of life at birth, a stage which appears to have been reached in the U.S.A. by both white and non whites.

2 In developing populations and in many western populations, life expectation at birth is still increasing, the rate of increase is regulated largely but not wholly by the fall in mortality rate of the young.

3 At late middle age there have been disappointingly small gains in life expectation over a period of three centuries, if not longer. In some populations — e.g. Jews in the U.S.A.⁵ and Indians in South Africa⁶ — life expectation at late middle age has declined.

All this is little realized and as Burch³ emphasized is happening in spite of the billions spent on medical services and research.

Alexander R P Walker, D.Sc.
South African Medical Research Council
Human Biochemistry Research Unit
South African Institute for Medical Research
Johannesburg, South Africa

REFERENCES

- 1 Psalm 90 v 10. The Holy Bible. King James Version.
- 2 Burch, G. E. People live no longer any more. *AM HEART J* 83:285 1972.
- 3 Weisler, H. The investigation of mortality. *Ann Life Insur Med* 1:3 1962.
- 4 Wallace, J. H. Human longevity. *Med J Aust* 1:442 1940.
- 5 Population census 6 Sept. 1960. Miscellaneous characteristics according to age—all races. Vol 9. Pretoria 1968. Government Printer.

- of the mucoid infiltrations *J Pathol* 63:503 1951
- 4 Fowler N O Gueron M and Rowlands D T Jr Primary myocardial disease *Circulation* 23:498 1961
- 5 Rossi J and Liscano L I Basophilic (mu-

coid) degeneration of myocardium A disorder of glycogen metabolism *Am J Pathol* 61:99 1910

- 6 Holleman L W J Van der Hart J A and de Vries G A M Type IV glycogenosis *Lab Invest* 15:357 1966

Cardiac causalgia and hoarseness

The syndrome of cardiac causalgia in major and minor forms has been described.^{1,2} The relationship of its manifestations to ischemic heart disease especially to myocardial infarction is well known. The development of hoarseness, however, is not recognized as one of the rare manifestations of this syndrome. Hoarseness is a symptom of cardiac causalgia is briefly illustrated by two recently observed patients.

N S H, a 60-year-old Caucasian woman developed an apical infarct in 1956. Since then she has experienced tightness in the chest on exertion. The tightness is associated with premature contractions, palpitation, dyspnea and sweating, but no cough. Recently the anginal episodes occurred more readily and more frequently. The pain developed after very little walking, emotional disturbance and excitement and disappeared with rest and sublingual use of nitroglycerin. The patient soon began to develop hoarseness and consulted two otolaryngologists, neither of whom found any vocal cord paralysis or any cause for the hoarseness. With strict and meticulous therapy the angina pectoris has subsided and so has the hoarseness.

S L G, a 70-year-old Caucasian woman developed an anteroapical infarct in 1965. Her recovery was uneventful except for a lupus erythematosus syndrome with LE phenomenon produced by quinidine and again by procainamide employed to control frequent premature contractions. Except for mild angina pectoris her cardiac state was satisfactory. During February 1970 she began to develop frequent episodes of angina pectoris with the slightest exertion. Anginal episodes were initiated by mild physical and psychic stress. One day in February she developed severe chest pain with dyspnea, coughing, palpitation and apprehension. Several days later she became hoarse as with a

laryngitis. She was confined to bed for a couple of weeks. After her angina pectoris and acute coronary insufficiency had subsided she consulted otolaryngologists who found her larynx and vocal cord to be normal. Nevertheless the hoarseness continued. With meticulous attention to therapy for ischemic heart disease the angina pectoris cleared by May 1970 and so did the hoarseness. With the disappearance of the anginal pain in June 1970 the hoarseness also disappeared. An otolaryngologist examined her on several occasions during that period and found no abnormalities.

In both patients nitroglycerin had been used on frequent occasion for the anginal pain and had relieved the angina but had no influence on the hoarseness. Steroids were not tried in either patient.

The mechanism for this syndrome remains unknown. Is it does the mechanism for cardiac causalgia is a functional disturbance. Both patients were treated for ischemic heart disease and advised that there was no organic laryngeal disease. As with classical cardiac causalgia their hoarseness gradually disappeared as they adhered closely to cardiac therapy.

G E Burch MD
Department of Medicine
Tulane University School of Medicine
1430 Tulane Ave
New Orleans, La 70112

REFERENCES

- 1 Burch G E Phillips J H and Delisquale N P Cardiac causalgia *Am Heart J* 67:75 1968
- 2 Burch G E and Giles T D Cardiac causalgia *Arch Intern Med* 125:809 1970

Decline and fall³

In the past three of the horse-men of the Apocalypse—War, Famine and Pestilence—saw to it that few reached adulthood and that fewer still attained old age. Of those who did not die young it was

believed that "The days of our years are three-score years and ten; and if by reason of strength they be four-score years, yet is their strength labour and sorrow." What are the days of our years at present?

Recently Burch³ provided evidence that people live no longer any more — and emphasized that far more research should be undertaken into the factors which regulate aging. His Annotation makes somber reading. He showed that in the U.S.A. expectation of life at birth increased enormously in the present century until about 1950 when it reached a plateau. He thought that the expectation may actually be declining.

Although in comparison with the past a far larger proportion of people nowadays live to a good age, it is not generally appreciated that expectation of life at late middle age has remained almost stationary as far back as records are available. Perhaps the earliest of life tables was constructed in 1687 by Halley⁴ of Halley's comet fame. He reported that in Breslau Germany expectation of life at 60 and at 80 years averaged about 12 and 5 years respectively. Three centuries later some correspond in data are as follows: Australians in 1955 17 and 6 years⁵; South African whites in 1960 17 and 6 years⁶; American Jews in 1965 15 and 5 years⁷. From this and other information it would seem that while expectation of life at birth in the U.S.A. reached its apparent maximum 20 years ago, expectation at late middle age in Caucasian populations over a very long period has slightly improved at age 60 years and virtually not at all at age 80 years. For the Jewish population of U.S.A. since 1940 there has been an undoubted decline.

From the graph given by Burch³ in the U.S.A. expectation of life at birth has remained steady since 1950 not only for whites but also for non-whites, the mean figure for the former is about 71 years and for the latter about 64 years, a difference of 7 years. This is very surprising. Most if not all would have predicted with as much accuracy that the difference would become progressively narrower with rise in the socioeconomic conditions of non-white. But this has not been the case. Burch³ considered the possibility that non-Caucasian races may be genetically programmed to have a shorter life span than whites. He regarded this as unlikely. Yet the possibility cannot be excluded. The most striking situation that comes to mind in this regard concerns Indians in India compared with Indians whose forebears emigrated to South Africa. In 1951 at Ramana garam in Mysore, South India, a general health study was made on a population of 73 000 rural Indians. It was found *inter alia* that of the leading causes of death the first ten were infections. Of persons 50 years or more 14.5 per cent reached 70 years or over. In South Africa the age structure of three random groups of urban Indians (330 families) living near Johannesburg has been studied. Almost all were in fairly comfortable circumstances. Leading causes of death among them were coronary heart disease, pneumonia, strokes, cancer and diabetes. Of persons aged 50 or more years only 9 per cent had reached 70 or more years. Although the number of families studied is relatively small, the results obtained are in agreement with the Census figures for 1950, namely 11 per cent for the half million Indian community in South Africa.⁸ But this figure has decreased since 1955, when it was 15 per cent.⁹ In this respect populations normally show an increase, not a decrease with time. Thus despite out-

wardly vastly improved environmental conditions South African urban Indians at late middle age have a somewhat lower expectation of life compared with their outwardly far less fortunate compatriots in rural India. In consonance with this information it is interesting to note that among urban dwellers both in India and in South Africa severe atheroma and peak frequency of myocardial infarction apparently occur a decade earlier in Indians than in whites.^{10, 11} Moreover in India there is evidence that urban dwellers in poor circumstances have a greater frequency of coronary heart disease than would be expected.¹² Nor is the situation described peculiar to South African Indians. In an investigation of 140 Malay families in a township in Johannesburg it was found that 85 per cent owned cars and 90 per cent had Bantu servants. Yet of persons 50 years or older only 9 per cent were 70 or more years of age. In comparison with the foregoing the corresponding proportion for South African whites in the 1960 Census was 22 per cent.¹³ In England and Wales in 1961 the proportion was 24 per cent.¹⁴ A further fact of importance is that among South African Bantu at a socioeconomic level far below that of local Indian and Malay the corresponding figure was relatively high, namely 17 to 18 per cent.¹⁵ It therefore appears that Indians have a malignant hyper-reactivity, possibly of genetic origin, to certain noxious factors which are linked with urban life.¹⁶

Briefly it would seem that

1. In contexts of modern life ethnic groups may differ markedly in their apparent maximum expectation of life at birth, a tag which appears to have been reached in the U.S.A. by both whites and non-whites.

2. In developing populations and in many western populations life expectation at birth is still increasing, the rate of increase is regulated largely but not wholly by the fall in mortality rate of the young.

3. At late middle age there have been disappointingly small gains in life expectation over a period of three centuries if not longer. In some populations — e.g. Jews in the U.S.A.⁷ and Indians in South Africa^{8, 9} — life expectation at late middle age has declined.

All this is little realized and as Burch³ emphasized is happening in spite of the billions spent on medical services and research.

Alexander R. P. Walker, D.Sc.
South African Medical Research Council
Human Biochemistry Research Unit
South African Institute for Medical Research
Johannesburg, South Africa

REFERENCES

1. Psalm 90 v. 10. The Holy Bible. King James version.
2. Burch G. E. People live no longer any more. *AM HEART J* 83: 285, 1972.
3. Wessler H. The investigation of mortality. *Ann Life Insur Med* 13: 1962.
4. Wallace V. H. Human longevity. *Med J Aust* 1: 412, 1910.
5. Population census 6 Sept. 1960. Miscellaneous characteristics according to age-all races. Vol 9. Pretoria 1968. Government Printer.

- 6 Fauman S J and Mayer A J Jewish mortality in the U S *Hum Biol* 41:416 1969
- 7 Rao S S and Rao S V A field study on local health services in Ramaniguram Mysore India Expert committee on Public Health Administration WHO/PIHA/30 17 Sept 1959 World Health Organisation Geneva
- 8 Population Census 6 May 1970 Sample tabulation Ages of Coloureds and Asians Report 02 01 02 Pretoria 1971 Government Printer
- 9 Population Census 8 May 1951 Ages-ill-rises Vol 5 Pretoria 1958 Government Printer
- 10 Padmavati S Epidemiology of cardiovascular disease in India II Ischaemic heart disease *Circulation* 25 711 1962
- 11 City of Durban Annual Report of City Medical Officer of Health for 1960 Durban 1961 City Health Department
- 12 Sivatham S G and Berry J V Prevalence of coronary heart disease in an urban population in northern India *Circulation* 3: 959 1968
- 13 Report of a working party of the College of General Practitioners *Br Med J* 11 655 1963
- 14 Walker A R I Coronary heart disease and future expectation of life *Circulation* 37:126 1968
- 15 Walker A R P Coronary heart disease—Are there differences in racial susceptibility? *Am J Epidemiol* 90 359 1969

Two hundredth anniversary of self-prediction of sudden, exertional cardiac death

William Heberden gave the first clinical description of angina pectoris to the College of Physicians on July 21 1768 but *Some Account of a Disorder of the Breast* was not published in the *Medical Transactions of the College* until February 1772. Later in Chapter 70 on *Pectoris Dolor* of a book written in Latin in 1782 and published posthumously in 1802¹ after it was translated into English by his son Heberden remarked that of an experience of nearly a hundred cases he had observed only one autopsy examination that of his 57 year old overweight anonymous physician A London physician Dr Unknown on reading Heberden's account was so impressed with the clarity of its presentation that he wrote a letter to Heberden in March 1772. Heberden's account of angina pectoris so exactly correspond (sic) with what I have experienced of late years that it determined me to give you such particulars as I can recollect at these times to have felt more especially as some sensations have frequently led me to think that I should meet with a sudden death. Dr Unknown described the phenomenon of enduring the pain (and continued my pace without indulging it) which Osler recognized in 1897² and MacAlpin and Kattus³ in 1966 described as walk through angina. Of other sensations which to me seem to indicate a sudden death he was uncertain whether they should be attributed to angina pectoris. He had often felt under various circumstances an universal pause within me of the operations of nature for perhaps three or four seconds and when she has resumed her functions I felt a shock at the heart. Since Heberden had mentioned in his initial report that several of his patients had died suddenly and were buried before he could examine them Dr Unknown left specific instructions that if he died suddenly Heberden should perform a postmortem examination.

In less than three weeks Heberden was informed

of the sudden death in less than half an hour of Dr Unknown who was in the midst of a walk which he was taking after dinner. Heberden obtained the services of Mr John Hunter and the autopsy was done within 48 hours. The patient exhibited great robustness. The contents of the thorax were examined with peculiar attention particularly the heart with its vessel and valves and all were found to be in a natural condition except some few specks of a beginning ossification upon the aorta. The left ventricle of the heart was remarkably strong and thick. It was remarkable that the blood was nowhere coagulated perfectly fluid being of the consistence of thin cream.

Heberden observed that other fellow sufferers noted the sensation of an apparent suspension of life for a few seconds while walking prior to death. As noted by Segall in 1944⁴ Dr Unknown described the cardiac arrhythmia as ventricular diastole of unusually long duration followed by a very strong heart beat. The patient correctly surmised that his syndrome was dangerous even though he never experienced cardiac pain at rest. That his sudden death was probably due to ventricular fibrillation is suggested by the fact that the postmortem examination failed to reveal any disease of the heart and its vessels and valves.

This year is the 200th anniversary of self prediction of sudden exertional cardiac death. Although sudden cardiac death is still very common the effectiveness of prompt defibrillatory treatment has been documented in 7 out of 7 cases of exertional cardiac arrest in patients with coronary heart disease. The lack of evidence of evolving myocardial infarction in at least 6 instances⁵ and the fact that the first of these patients now 64 years of age has continued physical training gainful employment and outdoor recreation activities without further recurrences of either myocardial infarction or car-

diagnosed for over 3 years testifies to Dr Claude Beck's comment about hearts too good to die

Robert A Bruce MD
Department of Medicine
Division of Cardiology
University of Washington
School of Medicine
Seattle Wash 98105

REFERENCES

- 1 Heberden William. Some account of a disorder of the breast. Med Trans R Coll Phys Lond 39 1772
- 2 Heberden William. Commentaries on the history and cure of disease. Translated by William Heberden Jr. London 1802
- 3 Osler W. Lectures on angina pectoris and allied states. New York 1897. J Appleton and Company p 52. Quoted by MacAlpin and Hattus⁴ p 183
- 4 MacAlpin R N and Hattus A A. Adaptation to exercise in angina pectoris. Circulation 33:183 1966
- 5 Segall H N. The first clinico-pathological case history of angina pectoris. Self-diagnosis by an anonymous physician. Autopsy by John Hunter. Reported by William Heberden in 1772. Bull Hist Med 18 102 1945
- 6 Bruce R A and Kluge W. Defibrillatory treatment of exertional cardiac arrest in coronary disease. JAMA 216 653 1971
- 7 Beck C S. Coronary artery disease. Am J Cardiol 1:38 1958

- 6 Irumu S J and Mayer A J Jewish mortality in the U S *Hum Biol* 41:116 1969
- 7 Rao S S and Rao S V A field study on local health services in Ramnagarim Mysore India Expert committee on Public Health Administration WHO/PIHA/30 17 Sept 1959 World Health Organisation Geneva
- 8 Population Census 6 May 1960 Sample tabulation Ages of Coloureds and Asians Report 02 01 02 Pretoria 1971 Government Printer
- 9 Population Census 8 May 1951 Ages-all races Vol 5 Pretoria 1958 Government Printer
- 10 Padmanabhi S Epidemiology of cardiovascular disease in India II Ischaemic heart disease *Circulation* 25:711 1962
- 11 City of Durban Annual Report of City Medical Officer of Health for 1960 Durban 1961 City Health Department
- 12 Sivatham S G and Berry J V Prevalence of coronary heart disease in an urban population in northern India *Circulation* 3: 939 1968
- 13 Report of a working party of the College of General Practitioners *Br Med J* ii 655 1963
- 14 Walker A R P Coronary heart disease and future expectation of life *Circulation* 3: 176 1968
- 15 Walker A R P Coronary heart disease—Are there differences in racial susceptibility? *Am J Epidemiol* 90 359 1969

Two hundredth anniversary of self-prediction of sudden, exertional cardiac death

William Heberden gave the first clinical description of angina pectoris to the College of Physicians on July 21 1768 but *Some Account of a Disorder of the Breast* was not published in the *Medical Transactions of the College* until February 1772. Later in Chapter 70 on *Pectoris Dolor* of a book written in Latin in 1782 and published posthumously in 1802¹ after it was translated into English by his son Heberden remarked that of an experience of 'nearly a hundred cases' he had observed only one autopsy examination that of his 52 year old overweight anonymous physician A London physician Dr Unknown on reading Heberden's account was so impressed with the clarity of its presentation that he wrote a letter to Heberden in March 1772. Heberden's account of angina pectoris 'so exactly correspond (sic) with what I have experienced of late years that it determined me to give you such particulars as I can recollect at these times to have felt more especially as some sensations have frequently led me to think that I should meet with a sudden death. Dr Unknown described the phenomenon of enduring the pain (and continued my pace without indulging it) which Osler recognized in 1897² and MacAlpin and Kattus³ in 1966 described as walk through angina. Of other sensations which to me seem to indicate a sudden death he was uncertain whether they should be attributed to angina pectoris. He had often felt under various circumstances 'an universal pause within me of the operations of nature for perhaps three or four seconds and when she has resumed her functions I felt a shock at the heart. Since Heberden had mentioned in his initial report that several of his patients had died suddenly and were buried before he could examine them Dr Unknown left specific instructions that if he died suddenly Heberden should perform a postmortem examination. In less than three weeks Heberden was informed

of the sudden death in less than half an hour of Dr Unknown who was in the midst of a walk which he was taking after dinner. Heberden obtained the services of Mr John Hunter and the autopsy was done within 48 hours. The patient exhibited great robustness. The contents of the thorax were examined with peculiar attention particularly the heart with its vessels and valves and all were found to be in a natural condition except some few specks of a beginning ossification upon the aorta. The left ventricle of the heart was remarkably strong and thick. It was remarkable that the blood was nowhere coagulated perfectly fluid being of the consistence of thin cream.

Heberden observed that other fellow sufferers noted the sensation of an apparent suspension of life for a few seconds while walking prior to death. As noted by Segall in 1944⁴ Dr Unknown described the cardiac arrhythmia as ventricular distole of unusually long duration followed by a very strong heart beat. The patient correctly surmised that his syndrome was dangerous even though he never experienced cardiac pain at rest. That his sudden death was probably due to ventricular fibrillation is suggested by the fact that the postmortem examination failed to reveal any disease of the heart and its vessels and valves.

This year is the 200th anniversary of self prediction of sudden exertional cardiac death. Although sudden cardiac death is still very common the effectiveness of prompt defibrillatory treatment has been documented in 7 out of 7 cases of exertional cardiac arrest in patients with coronary heart disease. The lack of evidence of evolving myocardial infarction in at least 6 instances⁵ and the fact that the first of these patients now 64 years of age has continued physical training gainful employment and outdoor recreation activities without further recurrences of either myocardial infarction or car

plantation but he made the initial world shattering successes possible. He was a quiet publicity shy but active clinical partner in a big world famous unit.

Recognition of his services was soon forthcoming. In 1959 he was appointed Director of the Council for Scientific and Industrial Research Cardiovascular Pulmonary Research Group at the University of Cape Town and in 1964 was appointed to a personal Associate Professorship of Medicine. In 1966 he was R. T. Hall guest lecturer in Australia and in 1967 was the Honored guest of the American College of Cardiology in Washington D. C.

Val Schrire was a fine clinical cardiologist. He trained himself to be precise and recorded and documented every clinical detail in the patients whom he saw. This started as a student and he kept carefully the clinical records and photographs of x-rays and ECG's of the patients he clerked as a student or treated as an intern and resident. He bound his early records in a series of books but an uncontrollable washing machine flooded his basement and damaged many of the later records. He built an outstanding personal collection of clinical information in the cardiac clinic. He took the histories himself, he evaluated them meticulously, elicited the physical signs carefully and then dissected the ECG and x-ray in detail. He dovetailed the clinical data always recording his comments and analyzing in detail any minor variation from an established clinical pattern. He was a clinical cardiologist and looked to the catheterization laboratory only for confirmation of his clinical assessment.

He worked hard and ran a fine unit. He did his work at a trot. He followed a simple dictum: he worked quickly and if his juniors were unable to keep pace they fell by the wayside. The good workers remained the indifferent postgraduates disappeared.

He had a passion for justice and priorities. He was intolerant of fools, sharp medical practice or indifferent patient care. His colleagues found that he offered the best clinical opinion and service to his patients but he was prepared to correct their errors.

He worked hard, often 10 to 14 hours a

day. He could see 40 to 50 patients a day in the outpatient clinic running swiftly from cubicle to cubicle. His working speed was unbelievable and occasional visitors were left breathless by his industry.

He made daily rounds and never failed to see a patient. For many years he also reported on all the hospital ECG's often at the end of a busy day. He had a photographic memory and could recall fine details long forgotten about patients who had been seen years before.

He was a delightful teacher and at his best in small groups. He spoke well, his argument and discussion were pertinent, he had an intimate knowledge of the published literature and he had a vast storehouse of information about unusual individual patients and he could trace their clinical records in minutes.

He was a human doctor, he seemed to have a cold exterior but he was warm and human to his patients and he could always remember their family details. He rarely forgot an item of clinical history and the patients would come back again and again, often having to wait for hours in a cold drafty corridor on a hard bench.

He made a big impact on cardiology although he made no major breakthroughs. He wrote classical descriptions of Beriberi and The natural history of pericarditis. His early research was concerned with pulmonary stenosis, the assessment of its severity and the detection of an associated ventricular septal defect. With Vogelbeil he studied the problem in detail and published the first important studies on the influence of vasoactive drugs on cardiac murmurs. He reviewed the clinical features of the common congenital and acquired disorders of the heart and studied the racial incidence of cardiac disease in the four different racial groups who live in the Western Cape. He was interested in the modification of the natural history of cardiac disease by an operation and made important long term studies in large groups of patients after correction of Fallot's tetralogy or after a valve replacement.

He wrote two important monographs. Clinical Cardiology has reached its third edition in seven years and with Professor C. N. Barnard he wrote The Surgery of

Obituary

Velva Schrire, M.D., F.R.C.P., F.A.C.C.

1917-1972



Dr Velva Schrire 1917-1972

Val Schrire has passed and has left a hiatus in cardiology in South Africa. He was a brilliant scholar matriculating in 1933 as the top student in South Africa. He graduated M.Sc. in 1938, Ph.D. in 1940 and M.B. Ch.B. (Honours) in 1941. He entered the armed forces and served from 1943 to 1945. He returned to Groote Schuur

Hospital to complete a postgraduate medical residency and in 1949 was appointed senior registrar to Paul Wood at the National Heart Hospital. This was followed by a short spell under Dr. Samuel Levine at the Peter Bent Brigham Hospital.

In 1951 he returned to Groote Schuur Hospital, Cape Town, and founded the cardiac clinic. For many years the clinic occupied a single room and this he shared with a secretary, a technician, a nurse, and the patients. The room served as a clinic during the day, an electrocardiographic reporting room in the late afternoons, and as a repository for records. Gradually, he was allocated more space, a room at a time and often corridors were enclosed to provide space for filing. He even shared his catheterization laboratory with the radiology department and only had its use for half of each day.

The clinic grew under his guidance and acquired an international reputation. It is now the finest clinical unit in the Southern Hemisphere and has few rivals. It has trained many clinical cardiologists, it has provided an unrivaled service to the entire country and patients come from all the major centers in South Africa.

Dr. Schrire was responsible for the development of a flourishing unit for cardiac surgery. The diagnosis in patients submitted to surgery was invariably complete and the surgical staff had only to close a defect or correct a valvular deformity. He nurtured, trained, cajoled, guided, and where necessary corrected his surgical colleagues. He personally was opposed to heart trans-

Letters to the Editor

The reliability of the Holter Avionics system in reproducing the ST T segment

To the Editor

The Holter Avionics system is used for long term recording of the electrocardiogram (ECG) under dynamic conditions. The system consists of three main parts: (1) a portable tape recorder which records the ECG of the examinee (Electrocardiocorder); (2) an oscilloscope on which the ECG signals recorded by the tape are displayed by rapid superposition (Electrocardioscanner) and (3) a unit for printout of the ECG complexes from the tape onto conventional ECG paper (Electrocardiocharter). This system is widely used for detecting transient disturbances in heart rate and rhythm.¹⁻³ Reports on its use for detection of changes in the ST T segment are scanty, probably because of the claim of Hinkle and co-workers⁴ that this system introduces artifacts in the ST T segment.

In a previous investigation⁵ using the Holter Avionics system we examined the ECG of 39 normal individuals around the clock and did not detect any deviations or artifacts induced by the recording system. Therefore we decided to test the reliability of the system by the following method. The ECG of 3 individuals with normal ECG and 3 patients with ischemic ST T changes was recorded through the usual precordial lead of the Holter Avionics system simultaneously by both the magnetic tape of the Electrocardiocorder (Model F) and by the

conventional Burdick ECG machine incorporated in the Electrocardiocharter. Thereafter the recording from the magnetic tape was transferred onto the Electrocardiocharter and the ECG complexes were again printed out on the Burdick machine. Comparing the ECG complexes recorded by the two methods showed a complete similarity except for a slight decrease in the height of the R wave on the tracing obtained through the Electrocardiocorder possibly due to the diminished high frequency of this machine. The similarity of the tracings is demonstrated in Figs 1 and 2.

We conclude therefore that the Holter Avionics system can be accepted as reliable for recording accurately the ST T segment and can be used for evaluation of dynamic changes induced by ischemia.

Shlomo Stern MD

Dan Tironi MD

Cardiology Service

Hadassah-Hebrew University Medical Center

Jerusalem, Israel

REFERENCES

1. Gilson J S, Holter N Y and Glasscock W R. Clinical observations using the electrocardiocorder—VSEP continuous electrocardiographic system. Tentative standards and typical patterns. *Am J Cardiol* 14:204, 1964.
2. Corday E, Banka V, Lang T W, Pappelbaum S, Gold H and Bernstein H. Detection of phantom arrhythmias and evanescent electro-



Fig. 1 Normal individual. Upper panel: ECG recorded directly on the Burdick ECG machine. Lower panel: ECG recorded on the magnetic tape of the Electrocardiocorder and subsequently printed out on the Burdick ECG machine.

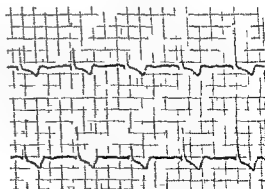


Fig. 2 Patient with ST T changes. Upper panel: ECG recorded directly on the Burdick ECG machine. Lower panel: ECG recorded on the magnetic tape of the Electrocardiocorder and subsequently printed out on the Burdick ECG machine.

the Common Congenital Cardiac Malformations,' which has been translated into four languages

His greatest contribution was in teaching and in the dissemination of personal knowledge to his students registrars, and colleagues Unlike many of his contemporaries, he did not like being a visiting professor and preferred to remain at home, at work providing a service to his patients and colleagues

Although he worked hard he relaxed at home on Sundays in the garden with his family He was a good father and husband and his family have been deprived prematurely of a good and loving companion

It is tragic that his last year was filled with suffering and pain He remained cheerful and continued to work to the end tending the clinic, disposing of patients, and completing his unpublished work

He died as he lived a quiet and humble but a very great man

Mervyn S Gotsman, M D

SIGNIFICANT IMPORTANT PUBLICATIONS

- 1 Schrire V The racial incidence of heart disease at Groote Schuur Hospital Cape Town *Am Heart J* 56 280 and 742 1958 59 335 1960
- 2 Schrire V Experience with pericarditis at Groote Schuur Hospital Cape Town *S Afr Med J* 33 810 1959
- 3 Schrire V and Gant J The electrocardiographic changes associated with benign heart disease *S Afr J Lab Clin Med* 5 195 1959
- 4 Vogelpoel L Nellen M Swanepoel A and Schrire V The use of amyl nitrite in the diagnosis of systolic murmurs *Lancet* 2 810 1959
- 5 Vogelpoel L and Schrire V Auscultatory and phonocardiographic assessment of pulmonary stenosis with intact ventricular septum *Circulation* 22 55 1961
- 6 Vogelpoel L Schrire V Beck W Nellen M and Swanepoel A The atypical systolic murmur of minute ventricular septal defect and its recognition by amyl nitrite and phenylephrine *Am Heart J* 62 101 1961
- 7 Vogelpoel L and Schrire V Auscultatory and phonocardiographic assessment of Fallot's tetralogy *Circulation* 22 73 1960
- 8 Schrire V and Vogelpoel L Atrial septal defect *Am Heart J* 68 305 1964
- 9 Schrire V Vogelpoel L Beck W Nellen M and Swanepoel A Ventricular septal defect. The clinical spectrum *Br Heart J* 27 813 1965

Letters to the Editor

The reliability of the Holter Avionics system in reproducing the ST T segment

To the Editor

The Holter Avionics system is used for long term recording of the electrocardiogram (ECG) under dynamic conditions. The system consists of three main parts: (1) a portable tape recorder which records the ECG of the examinee (Electrocardiocarder) (2) an oscilloscope on which the ECG signals recorded by the tape are displayed by rapid superposition (Electrocardioscanner) and (3) a unit for printout of the ECG complexes from the tape onto conventional ECG paper (Electrocardiocharter). This system is widely used for detecting transient disturbances in heart rate and rhythm.¹⁻⁴ Reports on its use for detection of changes in the ST T segment are scanty, probably because of the claim of Hinkle and co-workers⁵ that this system introduces artifacts in the ST T segment.

In a previous investigation⁶ using the Holter Avionics system we examined the ECG of 39 normal individuals around the clock and did not detect any deviations or artifacts induced by the recording system. Therefore we decided to test the reliability of the system by the following method. The ECG of 3 individuals with normal ECG and 3 patients with ischemic ST T changes was recorded through the usual precordial lead of the Holter Avionics system simultaneously by both the magnetic tape of the Electrocardiocarder (Model E) and by the

conventional Burdick ECG machine incorporated in the Electrocardiocharter. Thereafter the recording from the magnetic tape was transferred onto the Electrocardiocharter and the ECG complexes were again printed out on the Burdick machine. Comparing the ECG complexes recorded by the two methods showed a complete similarity except for a slight decrease in the height of the R wave on the tracing obtained through the Electrocardiocarder possibly due to the diminished high frequency of this machine. The similarity of the tracings is demonstrated in Figs 1 and 2.

We conclude therefore that the Holter Avionics system can be accepted as reliable for recording accurately the ST T segment and can be used for evaluation of dynamic changes induced by ischemia.

Shlomo Stern M.D.

Dan T. Nons M.D.

Cardiology Service

Hadassah Hebrew University Medical Center
Jerusalem, Israel

REFERENCES

1. Gilson J. S., Holter N. Y. and Glasscock W. R. Clinical observations using the electrocardiocarder—VSEP continuous electrocardiographic system. Tentative standards and typical patterns. *Am J Cardiol* 14:204, 1964.
2. Corday E., Bazuka V., Lang T. W., Pappelbaum S., Gold H. and Bernstein H. Detection of phantom arrhythmias and evanescent electro-

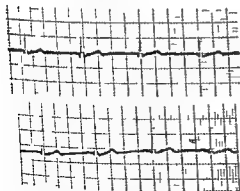


Fig. 1 Normal individual. Upper panel ECG recorded directly on the Burdick ECG machine. Lower panel ECG recorded on the magnetic tape of the Electrocardiocarder and subsequently printed out on the Burdick ECG machine.

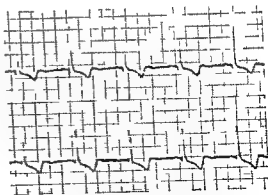


Fig. 2 Patient with ST T changes. Upper panel ECG recorded directly on the Burdick ECG machine. Lower panel ECG recorded on the magnetic tape of the Electrocardiocarder and subsequently printed out on the Burdick ECG machine.

cardiographic abnormalities. Use of prolonged direct electrocardiogram. *JAMA* 193:417, 1965

- 3 Stern S, Ben Shachar G, Tzivoni D and Braun K. Detection of transient arrhythmias by continuous long term recording of electrocardiograms of active subjects. *Isr J Med Sci* 6:103, 1970
- 4 Silverman M E and Flamm M D Jr. Variant angina pectoris. Anatomic findings and prognostic implications. *Ann Intern Med* 75:339, 1971
- 5 Hinkle J F, Meyer J, Stevens M and Carver S T. Tape recording of the LCG of active men. Limitations and advantages of the Holter Avionics instruments. *Circulation* 36:752, 1967
- 6 Tzivoni D. The electrocardiogram during sleep. M.D. thesis, Jerusalem 1971. Hebrew University-Hadassah Medical School

Hypertrophic obstructive cardiomyopathy

To the Editor

Hypertrophic obstructive cardiomyopathy (HOCM) is a disease which has attracted wide spread interest but whose natural history remains poorly understood.¹⁻⁴ Recently it has become apparent that the diagnosis may be made in elderly patients in whom it was clinically unsuspected.⁵ We report here a lady with long standing cardiac symptoms in whom the diagnosis of HOCM was not made until her seventy seventh year.

F.C. is now a 79 year old Caucasian woman who was admitted to the hospital in July 1970 because of retrosternal pressure sensations and syncopal attacks. At age 4 her parents were told that she had rheumatic fever and her activities were restricted throughout childhood and young adulthood. She was first told she had a heart murmur when she was 35 years old. She retired from school teaching when she was 51 because of progressive exertional dyspnea and fatigue. During the next 21 years she became short of breath performing routine household chores and developed retrosternal pressure sensations consistent with angina pectoris and transient bouts of lightheadedness associated with exertion. She was treated with digitalis, salt restriction and diuretics without apparent success. In the week prior to admission her retrosternal pressure sensations became more frequent, more prolonged and refractory to nitroglycerine. She also experienced syncopal episodes while straining at the toilet.

On examination she was a thin elderly lady with a blood pressure of 130/80 and heart rate of 75 per minute. The carotid pulse upstroke was bifid and hyperdynamic. The second heart sound was normal and an atrial gallop was heard. The heart was enlarged and there was a Grade III/VI systolic murmur heard all over the precordium and radiating into both the carotid and axilla. A few inspiratory rales were heard at both base. There was no hepatosplenomegaly or peripheral edema.

The electrocardiogram (ECG) showed first degree heart block and left ventricular hypertrophy. The chest x-ray revealed cardiomegaly and calcification of the aortic arch. Routine laboratory studies were normal. The levels of epinephrine and norepinephrine in the urine were respectively 96.3 and 60.1 ng per minute approximately three times normal for our laboratory.

An echocardiogram showed definite anterior movement of the anterior mitral leaflet during systole.⁶ An apex phonocardiogram demonstrated the presence of a fourth heart sound and an early systolic murmur. Right and transseptal left heart catheterization were performed. Both cardiac output and stroke volume were subnormal. A peak systolic pressure gradient was recorded between the left ventricle and the brachial artery at 95 mm Hg and the systemic arterial pulse showed bifurcated pattern with a classical double hump between the peak and the diastolic notch. Left ventricular angiography showed massive symmetrical thickening of the wall of the left ventricle and a normal aortic valve. Based on the above findings a diagnosis of HOCM was made.

While in the hospital digitalis was stopped and the patient begun on propranolol 40 mg per day. In the year and a half since discharge the patient has done well on propranolol and furosemide 40 mg every other day. She no longer has syncope or retrosternal pressure sensations. Although her exercise tolerance has not improved, she has noted an increased sense of well being. At the time of this writing (April 1972) she is feeling fine.

The medical histories of 29 family members in five generations were obtained. We examined six relatives because of symptoms suggestive of heart disease, none of whom had evidence of HOCM by physical examination, chest fluoroscopy or ECG.

This lady's case history is enlightening in that it illustrates how HOCM may be present in the elderly who have been considered to have other forms of heart disease for many years. She is unique because she is the oldest patient yet reported with this condition and because of the long relatively benign course of her illness.

Laurence I. Jacobs MD

Robert D. Lee MD

Paul A. Yu MD

Department of Medicine

University of Rochester Medical Center

Rochester, N.Y. 14642

REFERENCES

- 1 Cohen J, Effat H, Goodwin J et al. Hypertrophic obstructive cardiomyopathy. *Br Heart J* 26:16, 1964
- 2 Frank S and Braunwald E. Idiopathic hypertrophic subaortic stenosis. Clinical analysis of 176 patients with emphasis on the natural history. *Circulation* 37:759, 1968
- 3 Parker M M. The course in idiopathic hypertrophic muscular subaortic stenosis. *Ann Intern Med* 70:903, 1969
- 4 Swan D A, Bell B, Oakley C M et al. Analysis of symptomatic course and prognosis

- and treatment of hypertrophic obstructive cardiomyopathy. *Br Heart J* 33:613 1971
5. White R, B Powell W, Jr, Dinmore P, E, et al. Idopathic hypertrophic subaortic stenosis in the elderly. *N Engl J Med* 280:196 1969
6. Ah, P, W Grams R, and Kramer D H. (Trans) and localization of left ventricular out flow obstruction in hypertrophic obstructive cardiomyopathy. *Circulation* 30:3 1967

Trends in training physicians

To the Editor

I know with interest and disagreement that the educators of America consider a general but adequate knowledge of medicine impossible—in short there is too much to learn. In view of the extent of the mass of knowledge known by the brains of even the superior and highly selected youths of America are unable to cope with it all. The solution is offered by the educators to the problem of their overabundance of knowledge is to reduce the length of time devoted to learning medicine. They give up the lecture to reduce the training period to three or four years. Some shout with pride that they train "interns" in 1 year or even one and one half years. In fact some do not even have to learn much at all to become physicians and train.

The emphasis is on the quantity of doctors produced. The advocate of the plan fails to realize that such a practice will only produce an extra year or two of graduates and then the shortened learning period will not even produce greater number only a qualified physician.

Our Russian counterparts realize there is more to learn and that a longer period is required to learn it. They therefore have increased their training period from 5 to 7 years. They emphasize quality scholarship, pursuit of research. We reduce our learning time from 4 to 2 years or even 1½ years and emphasize quantity.

Our shortsighted attitude and practice continue to decrease the level of world medicine will move from America to Russia within the next 10 to 20 years. Patients of all countries will look to Russia for special care and the youths of the world will seek Russian diplomas, certificates of special training, and advanced education.

Why not emphasize quality scholarship, pursuit and research as well as quantity? Why not 500 more medical schools with classes of only 75 students or less with adequate scholarship of medicine teachers? Why do we medical school and educators express pride in their small classes (75 or fewer students) less than 10 years ago but now large classes are the thing of the time? Our money is the answer? Yes, but what about sick people and lives. With all the great advancements of modern times people still long to live longer but it is no longer anymore.

If you could only help to awaken the educator

G. E. Burch MD
Tulane University
School of Medicine
New Orleans La

REFERENCES

1. Burch G E. There is not too much to learn. *Am J Cardiol* 22:137 1968
2. Muller E, Wokosch G, Buller F, T Hess L, Tetu D and Luchberg R O. The Soviet health system—Aspects of relevance for medicine in the United States. *N Engl J Med* 286:693 1972
3. Burch G E. People live no longer anymore. *Am Heart J* 83:35 1971

Atrioventricular interaction in isorhythmic dissociation

To the Editor

In November 1971 and in January 1972 Levy, Damato and Bolsh¹ and Luly² and I³ published two papers referring to the mechanism of synchronization in dogs and in man respectively in this journal. From our own studies on this subject carried out on cat⁴ and from previous observations in patients with artificial cardiac pacemakers⁵ we can confirm the findings of these authors in most points of view. There are some striking differences, however, with respect to the effect of atrial stretch. Since Damato and co-workers do not know our papers from 1965 and 1969 we should be glad to give some comments to the problem mentioned above.

The experiments were carried out in 52 anesthetized cats which remained in spontaneous respiration. Right ventricular pacing was performed by a transvenous approach. Aortic pressure, right atrial pressure and right atrial ECG were studied in every case. Like Damato and co-workers and in contrast to Levy and Lulek we preferred to study the mechanism of synchronization in animals with intact A-V conduction systems. Five cats were studied which previously had been treated with reserpine vagotomy and as performed in 26 cats and beta adrenergic blockade with propranolol was done in 9 cats. In five cats experiments were carried out with constant aortic pressure and in eight others with constant right atrial pressure.

Our results were similar to those of Damato and co-workers¹ and of Levy and Lulek² with respect to the changes in aortic and right atrial pressure and with respect to the frequency in the appearance of synchronization phenomena. In contrast to Levy and Lulek² however synchronization did not cease when the aortic pressure was kept at a constant level.

To illustrate we may be allowed to represent a segment of an original experiment in which the decrease of aortic pressure during asynchronous ventricular pacing was prevented by uncoupling a tube leading from the central aorta to a reservoir elevated to a height equivalent to the prevailing mean aortic pressure (Fig. 1). At arrow 1 ventricular pacing begins with a rate little above the spontaneous sinus rate. At arrow 2 the ventricles become depolarized by the artificial pacemaker whereas the atria are excited on a retrograde pathway. An increase of right atrial pressure can be observed whereas the aortic pressure remains constant. At arrow 3 the rate

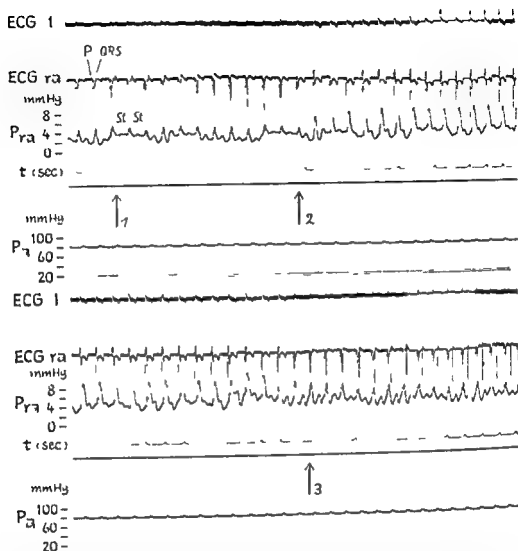


Fig 1 Section from synchronization experiment No 164 (aortic pressure at a constant level) Spontaneous sinus rate 67 per minute pacing frequency 69 per minute ECG 1 = ECG Lead I ECG ra = right atrial ECG P_{ra} = right atrial pressure P = aortic pressure Time marker (t) denotes seconds The records of the top half of this figure are continued in the bottom portion

of sinus node has exceeded the fixed pacemaker rate the temporal relationship between atrial and ventricular contraction has normalized and the atrial pressure decreases. Under these hemodynamic conditions the frequency of the sinus node begins to decelerate toward its initial value. If the pacemaker rate always is drawn near the accelerated sinus rate synchronization can develop as described by Levy and Zieske⁴ and by Paulay, Damato and Bobb⁵.

Fig 2 demonstrates a diagrammatic representation of the whole experiment a segment of which was shown in Fig 1. Depolarization of the ventricles prior to the atria (hatched field) leads to sinus rate increase. After this period sinus rate begins to decrease.

There is another argument which confirms our assumption that arterial blood pressure fluctuations cannot be the crucial mechanism of synchronization. Frequent atrial pacing leads to decrease in aortic pressure too (by insufficient diastolic filling of the

ventricles) but sinus rate does not increase. On the contrary there is to be observed a decrease in sinus rate.

In agreement with Paulay, Damato and Bobb⁵ we suggest that stretching of the sinus node fibers plays the most important role in accelerating sinus rate. Effective stretch however cannot be produced by extension of the entire atrial wall as elucidated from our experiments with constant right atrial pressure (see Fig 13 and Table VIII in our article from 1969⁶). The crucial mechanism of sinus rate acceleration which may lead to synchronization of atria and ventricles in animals and in men is in our opinion stretching of sinus node fibers by atrial contraction against the closed tricuspid valve.

Karl W Diederich Priv Do MD
Hasib Djonlagic MD
II Medical Clinics Medical School of Lubeck
University of Kiel
24 Lubeck West Germany

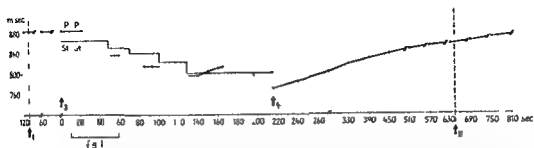


Fig 2 Diagrammatic representation of synchronization experiment No 164 At arrow 1 the aortic pressure fluctuations were attenuated by unclamping a tube connecting the central aorta with an elevated reservoir At arrow 2 the clamp was reapplied Arrow 3 demonstrates the beginning and arrow 4 the end of artificial pacing

REFERENCES

- 1 Diederich K W and Hoffmeister H E Synchronisationsphänomene am Herzen mit elektrischem Schrittmacher *Z Kreislaufforsch* 54 489 1965
- 2 Diederich K W Untersuchungen zum Frequenzanleich zwischen Sinusrhythmus und elektrischem Pacemaker Rhythmus *Verh Dtsch Ges Kreislaufforsch* 35 218 1969
- 3 Diederich K W Synchronisation mechanisms bei spontaner und induzierter Vorhof-Kammerdissociation und ihre Analyse *Arch Kreislaufforsch* 60:154 1969
- 4 Levy M N and Zieske H Mechanism of synchronization in isorhythmic dissociation I Experiments on dogs *Circ Res* 27 429 1970
- 5 Paulay K L Damato A N and Bobb G A Atrioventricular interaction in isorhythmic dissociation *AM HEART J* 647 1971
- 6 Paulay K L and Damato A N Atrioventricular interaction in man during pacing induced isorhythmic dissociation *AM HEART J* 83 5 1972

Reply

To the Editor

We read with interest the data summarized in the letter above by Drs Diederich and Djonlagic. Our observations in dogs in which right atrial pressure was controlled by an atrial vent show the contribution of right atrial pressure changes to the mechanism of synchronization of atria and ventricles in isorhythmic dissociation (unpublished findings). The results of acute extrinsic cardiac denervation experiments (Reference 5 above) indicate that arterial baroreceptor reflexes are involved also. Thus we consider that both arterial and right atrial pressure change are important factors in the mechanism of A V synchronization in man.

Karlen L Paulay M D
Anthony N Damato M D
Gustavus A Bobb B S

Cardiopulmonary Laboratory
United States Public Health Service Hospital
Staten Island N Y 10304

Book reviews

STROKE REHABILITATION—A Guide to the Rehabilitation of an Adult Patient Following a Stroke By Harry F Zankel MD Springfield Ill 1971 Charles C Thomas Publisher 284 pp Price \$15.75

Stroke rehabilitation is an extremely important subject in medicine at the present time. Zankel presents rehabilitation primarily from the physical point of view. The book contains many good photographs of patients receiving various forms of physiotherapy. The text is rather loosely written however and lacks adequately detailed information. For example on page 138 no specific drugs are presented as to the type of drug to use etc. This should be used for thrombolytic therapy. The management of the shoulder hand syndrome is also lacking in specific details which are needed by the practicing physician. Although rehabilitation of the patient with a stroke is important this book is not very helpful because it deals with generalities.

ECG DIAGNOSIS: SELF ASSESSMENT By Edward K. Chung MD IACP FACC and Donald J. Chung MD Hagerstown 1972 Medical Department Harper & Row Publishers Inc 221 pages Price \$17.95

In this title clear illustrations of a wide variety of electrocardiograms are presented in a fashion to test the reader's ability to interpret ECGs. The authors present each tracing with a very brief clinical summary along with the ECG on one page and the interpretation on the reverse side. This manner of presentation allows the student to make his interpretations and then check them with the authors. The 200 ECGs are fairly common ones. However some are seldom encountered even in a busy internist's practice. A reader who can interpret these tracings properly would have a good knowledge of electrocardiography. This is a very good manual.

CIRCULATORY EFFECTS AND CLINICAL USES OF BETA ADRENERGIC BLOCKING DRUGS Edited by Donald C. Harrison MD Amsterdam 1971 Excerpta Medica 147 pp Price \$12.50

The use of beta adrenergic blocking drugs is increasing so rapidly it is therefore necessary that the physician be thoroughly acquainted with the mechanism of action of these drugs as well as their indications and value in various cardiac disease states. Harrison and his associates review the action of these drugs and their uses in 9 brief chapters. They discuss in about 140 pages the

pharmacology, circulatory effects, and use of the β drugs in angina pectoris, in arrhythmias, myocardial infarctions, hypertrophic subaortic stenosis, hypertension, hyperthyroidism, and other diseases. The contraindications and limitations are also presented. Unfortunately, their discussions of the use of these drugs in the various clinical states emphasize the drugs themselves but fail to indicate strongly the importance of integrating the administration of the drugs along with other important therapeutic measures such as diet, smoking, caffeine intake, digitalis, antiarrhythmic agents, and rest. The experienced clinician will find this short book more helpful than the beginner. The latter of course will learn much about these drugs in Harrison's book, but he must realize they represent only one cardiac agent. The publication is a good one.

THE SINUATRIAL PACEMAKER OF THE HEART By Chandler McC. Brooks and Hsin Hsiang Lu Springfield Ill 1972 Charles C. Thomas Publisher 119 pp Price \$15.00

This important short monograph should interest all students of medicine and physiology, but especially cardiologists and other physicians who have a special interest in cardiology. Brooks and his associates have had an interest in pacemakers of the heart for many years. The sinoatrial node is of special importance. The authors in less than 150 pages review the anatomy of the S-A node, development of the impulse, the electrophysiologic properties of the node and its response to various factors including pathologic states and arrhythmias. A good bibliography is included. Some of the historical comments are interesting, especially the role of Keith and Flack in the discovery of the S-A node. The illustrations are good and the discussion of action potential traces as influenced by various factors such as electrolyte concentrations are all recent important contributions. This is a very good and important book. It is especially timely in view of the relatively intense interest in electrophysiologic phenomena of the heart and the diagnosis and management of cardiac arrhythmias.

ACUTE CORONARY CARE By Gerald H. Whipple MD et al Boston 1972 Little Brown & Company 383 pp Price \$11.50

Several books and booklets have appeared recently on the CCU and the intensive care of the patient with acute coronary disease. Each one has its own features. This one is fairly extensive. It is

of value for nurses, other attendants and physicians. The authors emphasize the practical aspects of coronary care and present the various chapters to educate the beginners as well as the more experienced person. There is nothing really new in this monograph but it presents a good course in acute coronary care and progressive coronary care. The concept of the CCU, nature of coronary heart disease, anatomy and physiology of the heart and lungs, infarction, nursing, electrocardiography, arrhythmia, resuscitation and cardioversion are among the many aspects discussed. Dr Whipple's preface is interesting and the selected bibliography, illustrations and index are all good. This monograph is worth owning as well as worth studying especially by nurses but also by physicians as well.

CLINICAL CARDIAC ROENTGEN DIAGNOSIS By Alphonse Jacob M.D. St. Louis 1972 Warren H Green Inc 309 pp Price \$19.50

This short discussion of Clinical Cardiac Roentgen Diagnosis should be of interest to interns, residents and medical students as well as busy practitioners. The book of about 300 pages contains clear and well selected reproductions of roentgenograms supported by a lucidly written text. The book is liberally illustrated. There is nothing unique about the volume, however, its small size and brevity along with the many illustrations should interest physicians who wish to review cardiac roentgenography quickly. This is not a reference book but it is a good short treatment of the subject.

Book reviews

STROKE REHABILITATION—A Guide to the Rehabilitation of an Adult Patient Following a Stroke By Harry T Zankel MD Springfield Ill 1971 Charles C Thomas Publisher 284 pp Price \$15.75

Stroke rehabilitation is an extremely important subject in medicine at the present time. Zankel presents rehabilitation primarily from the physical point of view. The book contains many good photographs of patients receiving various forms of physiotherapy. The text is rather loosely written however and lacks adequately detailed information. For example on page 138 no specific data are presented as to the type of drug, dosage etc. that should be used for thrombolytic therapy. The management of the shoulder hand syndrome is also lacking in specific details which are needed by the practicing physician. Although rehabilitation of the patient with a stroke is important this book is not very helpful because it deals with generalities.

ECG DIAGNOSIS SELF ADMINISTRATION By Edward K. Chung MD IACP IACC and Donald K. Chung MD Hagerstown 1972 Medical Department Harper & Row Publishers Inc 221 pages Price \$12.95

In this atlas clear illustrations of a wide variety of electrocardiograms are presented in a fashion to test the reader's ability to interpret ECGs. The authors present each tracing with a very brief clinical summary along with the ECG on one page and the interpretation on the reverse side. This manner of presentation allows the student to make his interpretations and then check them with the authors. The 200 ECGs are fairly common ones. However some are seldom encountered even in busy internists' practice. A reader who can interpret these tracings properly would have a good knowledge of electrocardiography. This is a very good manual.

CIRCULATORY EFFECTS AND CLINICAL USES OF BETA ADRENERGIC BLOCKING DRUGS Edited by Donald C. Harrison MD Amsterdam 1971 Lacerpt Medica 147 pp Price \$12.50

The use of beta adrenergic blocking drugs is increasing constantly. It is therefore necessary that the physician be thoroughly acquainted with the mechanism of action of these drugs as well as their indications and value in various cardiac disease states. Harrison and his associates review the action of these drugs and their uses in 9 brief chapters. They discuss in about 140 pages the

pharmacology, circulatory effect and use of the "drugs" in angina pectoris, in arrhythmias, myocardial infarction, hypertrophic subaortic stenosis, hypertension, hyperthyroidism and other diseases. The contraindications and limitations are also presented. Unfortunately their discussions of the use of these drugs in the various clinical states emphasize the drugs themselves but fail to indicate strongly the importance of integrating the administration of the drugs along with other important therapeutic measures such as diet, smoking, caffeine intake, digitalis, antiarrhythmic agents and rest. The experienced clinician will find this short book more helpful than the beginner. The latter of course will learn much about the "drugs" in Harrison's book but he must realize they represent only one cardiac agent. The publication is a good one.

THE SINUATRIAL PACEMAKER OF THE HEART By Chindler McC Brook and Hsin Hsiung Lu Springfield Ill 1972 Charles C Thomas Publisher 149 pp Price \$15.50

This important short monograph should interest all students of medicine and physiology but especially cardiologists and other physicians who have a special interest in cardiology. Brook and his associates have had an interest in pacemakers of the heart for many years. The sinoatrial node is of special importance. The author in less than 150 pages reviews the anatomy of the SA node, development of the impulse, the electrophysiologic properties of the node and its response to various factors including pathologic states and arrhythmias. A good bibliography is included. Some of the historical comments are interesting especially the role of Keith and Flack in the discovery of the SA node. The illustrations are good and the discussion of action potential traces as influenced by various factors such as electrolyte concentrations are all recent important contributions. This is a very good and important book. It is especially timely in view of the relatively intense interest in electrophysiologic phenomena of the heart and the diagnosis and management of cardiac arrhythmias.

ACUTE CORONARY CARE By Gerald H Whipple MD et al Boston 1972 Little Brown & Company 383 pp Price \$14.50

Several books and booklets have appeared recently on the CCU and the intensive care of the patient with acute coronary disease. Each one has its own features. This one is fairly extensive. It is

Books received

RESEARCH IN DISEASES OF THE TROPICS—British Medical Bulletin Vol 28 No 1 January 1972
C L Gordon Smith Scientific Editor London
1972 The Medical Department The British Council
102 pages Price \$6 50

✓ CARL OF THE CRITICALLY ILL CHILD By R S Jones
M D and J B Owen Thomas MB ChB M D
Baltimore 1971 The Williams & Wilkins Company
323 pages Price \$20 75

✓ CHANGING CONCEPTS IN CARDIOVASCULAR DISEASE
Edited by Henry I Russek M D and Burton L
Zohman M D Baltimore 1972 The Williams &
Wilkins Company 469 pages Price \$23 75

✓ PERIPHERAL VASCULAR DISEASES Vol 4 By John I
Hurlburt II M D John L Furman M D and

John A Spittell Jr M D Philadelphia London
and Toronto 1972 W B Saunders Company 197
pages Price \$25 00

PLASMA LIPOPROTEINS Biochemical Society Sym-
posium No 33 held in University College London
April 1971 Edited by R M S Smelhe London and
New York 1971 Academic Press Inc 165 pages
Price \$8 95

HEART ATTACK YOU DON'T HAVE TO DIE BY
Christian Barnard New York 1971 Delacorte
Press 178 page Price \$6 95

✓ PROGRESS IN CARDIOLOGY By Paul N Yu M D
and John I Goodwin M D Philadelphia 1972
Lea & Febiger Publishers 283 pages Price \$15 00

Announcements

International Symposium on Cardiac Pacing

The 14th International Symposium on Cardiac Pacing will be held in Groningen, the Netherlands on April 17-19, 1973, in the Congress Centre Mar tinhal.

Organized by the State University of Groningen, the Dutch Society of Cardiology, and the Dutch Heart Foundation, the topic will include basic principles of cardiac stimulation, world survey of cardiac pacing systems, energy sources, electrodes, stimulation threshold, exceptional indications for cardiac pacing, interference ECGs in cardiac pacing, pacing in myocardial infarction, pacemaker clinics, and follow up systems. Each area will include a general survey and an outline of the latest development.

Fees will be 100 Netherlands florins (US \$50) for participants and 100 Netherlands florins (US \$50) for accompanying guests. For further information, please write Dr. H. J. Th. Thalen, Secretary General, Secretariat at Symposium on Cardiac Pacing, Dept. of Cardiology, University Hospital Groningen, the Netherlands.

Subspecialty Board on Cardiovascular Disease

Requirements for examination

A. PREREQUISITE

The candidate must be certified as a Diplomate in Internal Medicine or must have passed the Qualifying Written Examinations of 1969 or 1970 before applying for examination. The candidate may apply for the examination after completing six months of his second year of training in cardiovascular disease but he must complete his formal full-time training in cardiovascular disease before taking his Subspecialty Board Examinations. No additional applications are being accepted for the current oral examination.

During the period of January 1 through March 15, 1972, completed applications are being accepted for the new examination in Cardiovascular Disease. The written component of the examination will be held October 17, 1972, at various centers in conjunction with written examinations in other subspecialty fields. In addition to the written examination, candidates for the Subspecialty Board on Cardiovascular Disease must pass an oral examination to be administered after December 31, 1972. The oral examination will be given at smaller regional examination stations in addition to larger national examination stations.

Application for the examination to be offered on

October 16, 1973, should request an application form in January 1973.

B. TRAINING

Requirement for general internal medicine. The candidate must be certified as a Diplomate in Internal Medicine (or have passed the Qualifying Examinations of 1969 or 1970).

In regard to the training in the broad field of internal medicine, the *Policies and Procedures* of the American Board of Internal Medicine, December 1970, read as follows in their relationship to the requirements for the Certifying Examination in general internal medicine:

Important note on minimum aspects of requirements. The Board recommends that candidates receive three years of training in the broad field of internal medicine, whether they plan to practice internal medicine or a subspecialty. It is recognized that some candidates can undertake the examination with a minimum of two of the three years of training in general internal medicine. These exceptional candidates must obtain authorization from the director of their second year of training in internal medicine. The Board will request from the director documentation of such authorization during the process of evaluation of the candidate's application for the examination.

Requirement for cardiovascular training. The current requirements of the American Board of Internal Medicine for subspecialty certification adopted in 1970 are:

Two years of full-time graduate education in the subspecialty. (This education must be completed in a program approved for three years of residency in internal medicine by the Residency Review Committee in Internal Medicine under a physician competent in the subspecialty field. A period of education in another institution may be acceptable, however, the institution must have a recognized reputation for advanced educational programs in the subspecialty and provide this in an academic atmosphere.)

Except in the most unusual circumstances, the candidate for certification by the Subspecialty Board on Cardiovascular Disease should have devoted the equivalent of one of the two years in training to the broad area of clinical cardiovascular disease, including experience in the intensive care of patients with acute cardiovascular disorders.

The earlier policy involving diplomates initiating residency training in internal medicine before July 1, 1970, stipulated four years of training in internal medicine and cardiovascular disease after completion of an internship. Although only one year of specific cardiovascular training was required, most candidates had completed two years of training in cardiovascular disease. It is the policy of the American

can Board of Internal Medicine that if candidates have undertaken less than the required two years of appropriate subspecialty training their receipt ability will be decided upon by the Executive Committee after review of their training and other credentials. As already indicated these requirements specified in this paragraph apply to candidates initiating residency training in internal medicine before July 1, 1970.

C EXAMINATION

The subspecialty examinations in Cardiovascular Disease are designed to demonstrate that the candidate possesses certain specialized knowledge and has acquired particular skills that entitle him to be known as a consultant to other internists. Candidates will be required to pass both a written and an oral examination. The written examination will test the following areas:

(1) Normal and pathologic anatomy and physiology of the circulatory system

(2) Interpretation of electrocardiograms, cardiovascular roentgenograms and special procedures and techniques used in the study of cardiovascular problems. The candidate should be able to integrate the information from these sources in such a way as to lead logically to the proper diagnosis and treatment.

(3) Knowledge of the pharmacology including side effects and therapeutic applications of drugs used in the treatment of cardiovascular diseases

(4) Knowledge of the indications, contraindications and complications of other forms of treatment including surgery

(5) Familiarity with the several aspects of cardiovascular and cardiac pacing as well as other specialized techniques useful in non-operative therapy and/or diagnosis

(6) Interpretation of hemodynamic data obtained from the catheterization laboratory

(7) Familiarity with the medical aspects of cardiovascular surgery

(8) Knowledge of contemporary cardiovascular literature

(9) Competence in the general field of internal medicine

The oral examination will consist of the evaluation of two patients with cardiovascular problems.

(1) The candidate must be proficient in taking an accurate history and in performing a detailed physical examination

(2) The candidate must convincingly demonstrate to his Board examiners his ability to integrate and synthesize cardiovascular data and to serve as a consultant in cardiovascular disease to a well-trained internist.

D REFERENCES

The applicant must supply the name(s) of the director(s) of his training program and the Chief of the Department of Medicine and the Director of the Division of Cardiology in which the applicant holds appointments. One or more of these individuals will be requested to complete evaluation forms which will permit the reporting of the details of the candidate's training program and an evaluation of overall clinical competence.

E RE EXAMINATION

(1) The interval between examinations will be not less than one year.

(2) A candidate who has failed three written or two oral examinations of the Board of Cardiovascular Disease must present satisfactory evidence of the completion of additional formal training (at least one year of full-time training) before reapplication to examination.

REQUESTS FOR APPLICATION FORMS SHOULD BE ADDRESSED TO: Executive Director, American Board of Internal Medicine, 3930 Chestnut Street, Philadelphia, Pa. 19104.

...you'd see the reasons for starting antihypertensive treatment with

ALDACTAZIDE®

spironolactone 25 mg with hydrochlorothiazide 25 mg

Spironolactone is the only available direct competitive aldosterone antagonist—and it appears to block the action of aldosterone wherever aldosterone acts in the body →

With ALDACTAZIDE your patient benefits from additive antihypertensive actions. The antihypertensive effects of spironolactone and hydrochlorothiazide are approximately equal but are based on different physiologic mechanisms

It is important to note in this respect that triamterene has little or no antihypertensive action

Special advantage for the hypertensive patient with potential diabetes or gout—Unlike thiazides spironolactone lowers blood pressure without altering glucose or urate metabolism. In ALDACTAZIDE the combination often permits a reduction in the dose-related hyperglycemic or hyperuricemic effect of the thiazide component

With ALDACTAZIDE spironolactone helps maintain potassium balance. Potassium loss due to the thiazide component is minimized or eliminated

Special advantage for the digitalized hypertensive patient—Preventing potassium loss is especially critical in order to avert digital toxicity. Aldactazide should be given cautiously to patients with elevated serum potassium levels. Periodic determinations of serum potassium will guard against the possibility of either hyperkalemia or hypokalemia

When supplemental potassium is determined by frequent laboratory tests, the possibility of hyperkalemia or a decrease in glucose tolerance is less. In severe edema may have a increased response to low sodium diet and a patient on such as 15 to 20 mg of p.d. some aldactazide therapy. Supplemental potassium will be necessary. Such patients all precautions with glucocorticoids or

(onset of nausea, vomiting, dizziness, abdominal cramps) or a hypotensive episode, a patient should be given a dose of 1 to 2 tablets daily. In the case of severe hypotension, the dose should be reduced to 1 tablet daily. In the case of severe hypotension, the dose should be reduced to 1 tablet daily. In the case of severe hypotension, the dose should be reduced to 1 tablet daily.

Dosage and Administration—For essential hypertension, the daily dose is two to four tablets in divided doses. Adjust the dosage according to the response of the patient. Reduce the dosage of either a hypertensive agent or the dosage of a diuretic by 50 percent since Aldactazide potentiates the action of such drugs. For edema, initiate a diuretic and if such drugs are ineffective, initiate Aldactazide. In adults, the average daily dose is one to two tablets daily. In children, the daily dose of Aldactazide is 0.75 to 1.5 mg of Aldactone per body weight.

References: 1. Hollander W and others. C. C. Res. 5: 101-110 (1965). 2. Mendlowitz M and others. Am. Heart J. 67: 397-409 (March 1964). 3. Liddle GW and others (Editors). Aldosterone. Medical and Biological Systems. New York: N.Y. Medical Communications, Inc. 1969. 4. Crabbe J. Acta Endocrinol (Kbh) 47: 419-431 (Nov) 1964. 5. Liddle GW. Arch. Intern. Med. 102: 998-1004 (Dec) 1958. 6. Liddle GW. Ann. N.Y. Acad. Sci. 139: 466-470 (Nov 22) 1966. 7. Vail RL and others. J.A.M.A. 198: 1143-1149 (Dec 1) 1966. 8. Johnston JC and Gr. ble HG. Arch. Intern. Med. 119: 225-231 (March) 1967. 9. Nicksen M, Goodman LS and Gilman A (Editors). The Pharmacological Basis of Therapeutics, 4th Edition. New York: The Macmillan Company 1970. pp 731-732.

Manufactured by S.E. Inc., New York, N.Y. 10017. Aldactone and Aldactazide are registered trademarks of S.E. Inc. Aldactone is a registered trademark of S.E. Inc. Aldactazide is a registered trademark of S.E. Inc.

can Board of Internal Medicine that if candidates have undertaken less than the required two years of appropriate subspecialty training their acceptability will be decided upon by the Executive Committee after review of their training and other credentials. As already indicated these requirements specified in this paragraph apply to candidates initiating residency training in internal medicine before July 1, 1970.

C EXAMINATION

The subspecialty examinations in Cardiovascular Disease are designed to demonstrate that the candidate possesses certain specialized knowledge and has acquired particular skills that entitle him to be known as a consultant to other internists. Candidates will be required to pass both a written and an oral examination. The written examination will test the following areas:

(1) Normal and pathologic anatomy and physiology of the circulatory system

(2) Interpretation of electrocardiograms, cardiovascular roentgenogram, and special procedures and techniques used in the study of cardiovascular problems. The candidate should be able to integrate the information from these sources in such a way as to lead logically to the proper diagnosis and treatment.

(3) Knowledge of the pharmacology, including side effects and therapeutic applications of drugs used in the treatment of cardiovascular diseases.

(4) Knowledge of the indications, contraindications, and complications of other forms of treatment including surgery.

(5) Familiarity with the several aspects of cardiovascular and cardiac pacing, as well as other specialized techniques useful in non-operative therapy and/or diagnosis.

(6) Interpretation of hemodynamic data obtained from the catheterization laboratory.

(7) Familiarity with the medical aspects of cardiovascular surgery.

(8) Knowledge of contemporary cardiovascular literature.

(9) Competence in the general field of internal medicine.

The oral examination will consist of the evaluation of two patients with cardiovascular problems.

(1) The candidate must be proficient in taking an accurate history and in performing a detailed physical examination.

(2) The candidate must convincingly demonstrate to his Board examiners his ability to integrate and synthesize cardiovascular data and to serve as a consultant in cardiovascular disease to a well-trained internist.

D REFERENCES

The applicant must supply the name(s) of the director(s) of his training program and the Chief of the Department of Medicine and the Director of the Division of Cardiology in which the applicant holds appointments. One or more of these individuals will be requested to complete evaluation forms which will permit the reporting of the details of the candidate's training program and an evaluation of overall clinical competence.

E RE-EXAMINATION

(1) The interval between examinations will be not less than one year.

(2) A candidate who has failed three written or two oral examinations of the Board of Cardiovascular Disease must present satisfactory evidence of the completion of additional formal training (at least one year of full-time training) before reapplication to examination.

REQUESTS FOR APPLICATION FORMS SHOULD BE ADDRESSED TO Executive Director, American Board of Internal Medicine, 3930 Chestnut Street, Philadelphia, Pa. 19104.

